Mécanismes de résistance chez les bacilles à Gram négatif et impact sur le choix des nouveaux antibiotiques

NARA
Nationales Referenzlaboratorium zur Früherkennung neuer Antibiotikaresistenzen und Resistenzmechanismen

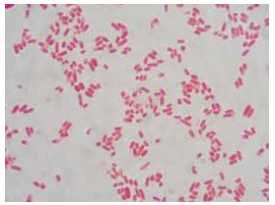
Instituts thématiques Inserm
Institut national de la santé et de la recherche médicale

French INSERM European Unit, University of Fribourg, Switzerland

Prof. Patrice Nordmann

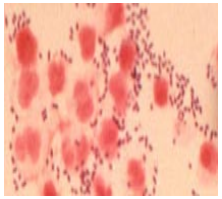
Clinically-relevant multidrug-resistant Gram negatives

Enterobacterales ***(E. coli, K. pneumoniae…)***



Pseudomonas aeruginosa

Acinetobacter baumannii

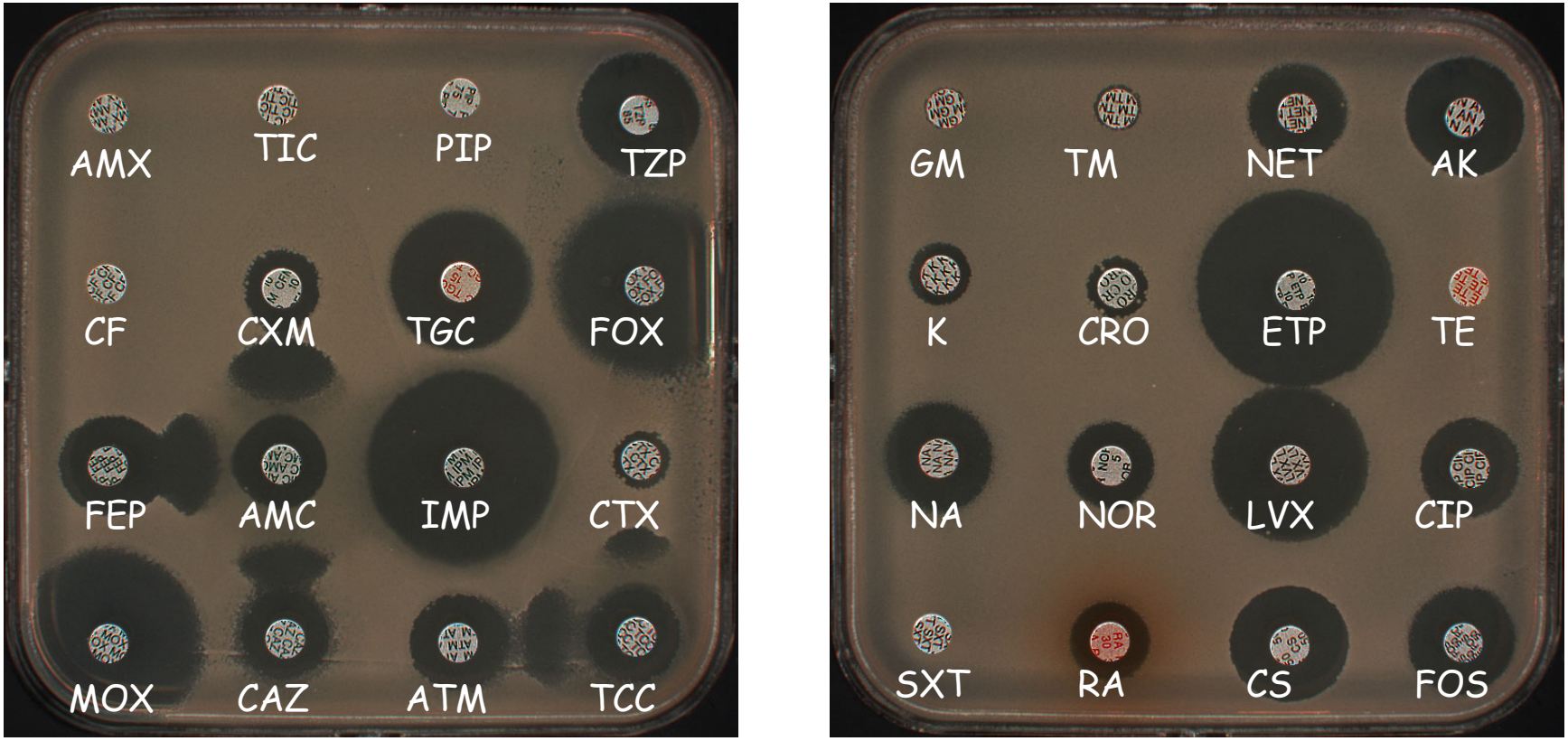


Extended-spectrum ß-lactamases in Gram negatives

Penicillins **Cephalosporins** **Carbapenems**

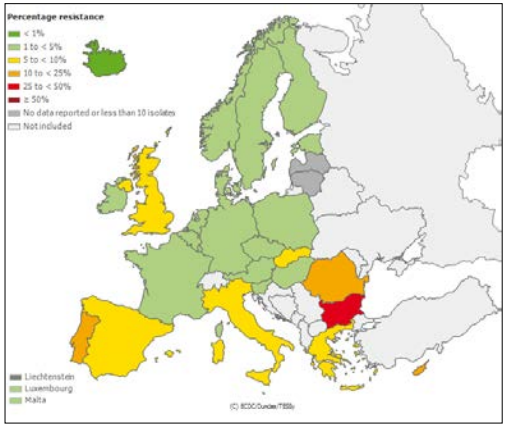
Extended-spectrum ß-lactamases (ESBL); CTX-M

Multidrug resistance of ESBL-producing *Escherichia coli*

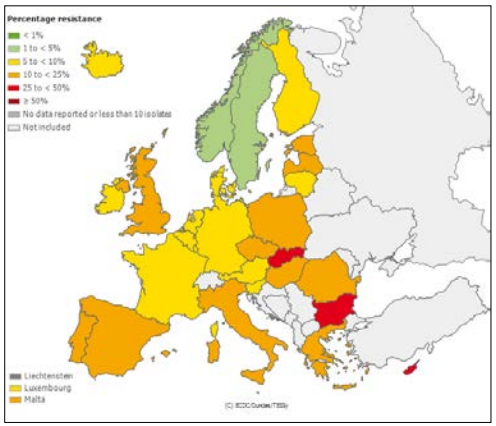


Enterobacteriaceae: Resistance to 3rd Generation Cephalosporins

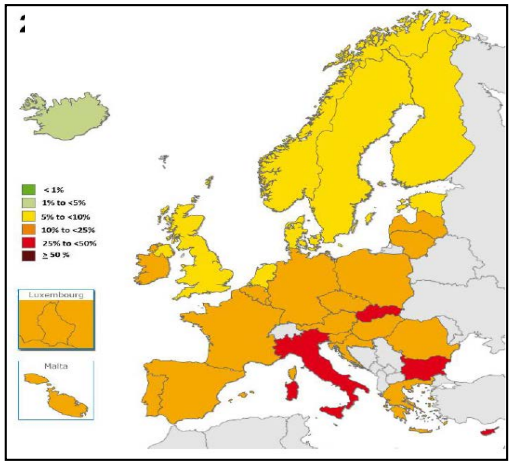
E.coli



2005

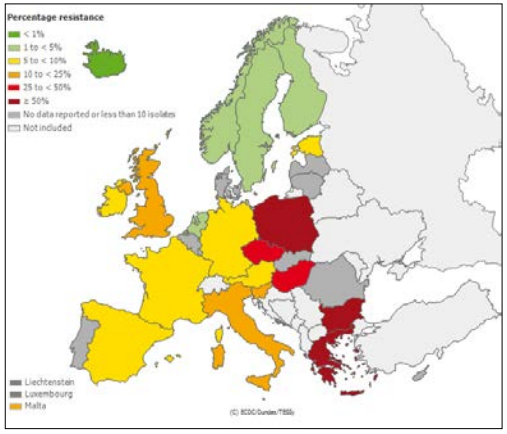


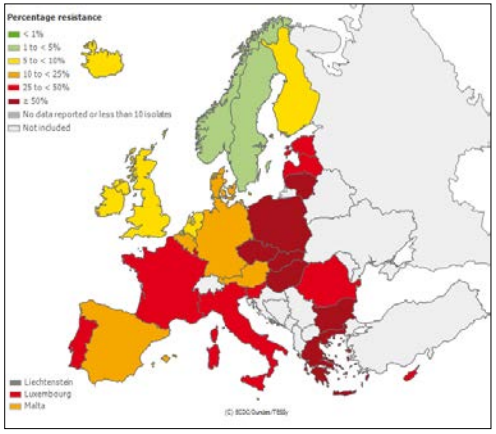
2011

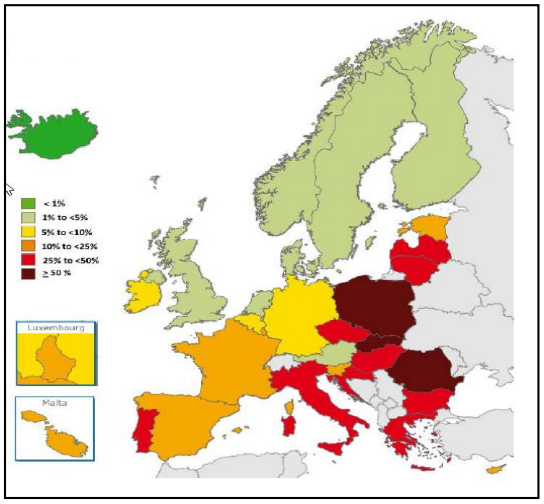


2016

K.pneumoniae







EARS-Net surveillance data, November 2017

Carbapenem Resistance: the most frequent mechanisms of resistance in Enterobacteriales

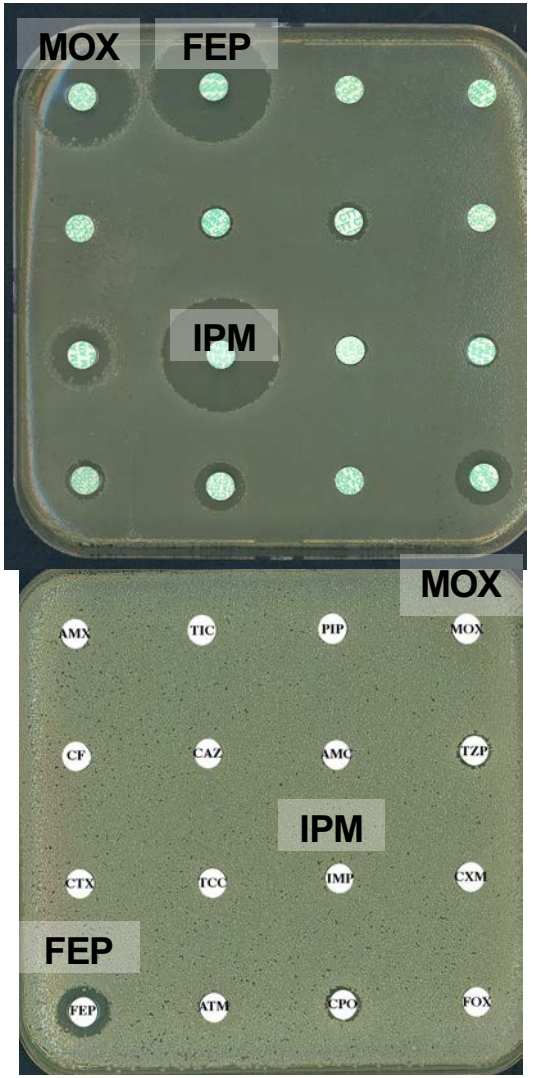
***Enterobacteriaceae* (++*Enterobacter* spp.)**

- Overproduced cephalosporinase
- Plasmid-mediated cephalosporinase
- Plasmid-mediated ESBL

Resistance to CIIIG

Decreased OM permeability

Additional Resistance to carbapenems

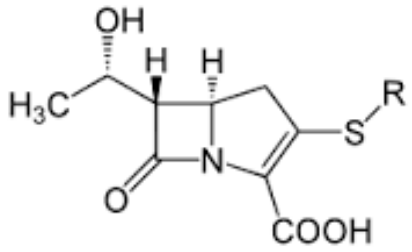


Lee EH, Nicolas MH, Kitzis MD, Pialoux G, Collatz E, Gutmann L. Association of two resistance mechanisms in a clinical isolate of Enterobacter cloacae with high-level resistance to imipenem.

Antimicrob Agents Chemother. 1991, 35:1093-8.

Important Emerging Resistances to Antibiotics

Carbapenems



Carbapenemases

Carbapenemases; triple difficulties

- Difficulty of detection
- Difficulty of treatment (owing to their multidrug-resistant character, with few drugs remaining active)
- Difficulty to limit their transmission and spread and therefore to control outbreaks (local, regional, national, pandemic).. Spread as a community-acquired pathogen

Emergence of carbapenemases in *Enterobacteriaceae* worldwide

NmcA
Enterobacter cloacae

1994
FRANCE
Naas, Nordmann
PNAS 1994: 91: 7693-7697

IMP-1
Serratia marcescens

1994
JAPAN
Osano, Arakawa, Wacharotayankun, Ohta, Horii, Ito, Yoshimura, Kato
AAC 1994 : 38: 71-78

KPC
Klebsiella pneumoniae

2001
USA
Yigit, Queenan, Anderson, Domenech-Sanchez, Biddle, Steward, Alberti, Bush, Tenover
AAC 2001 : 45: 1151-1161

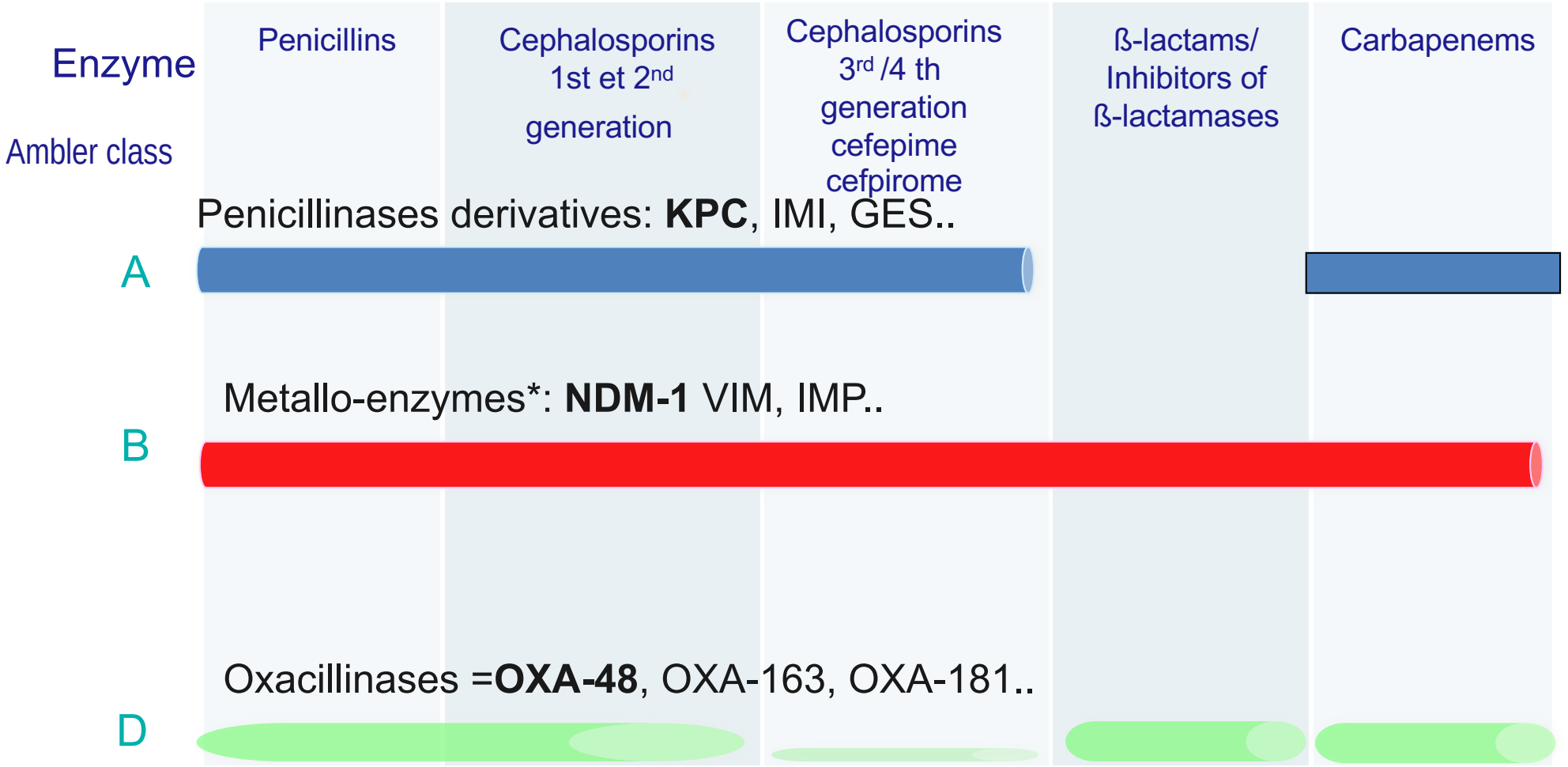
OXA-48
Klebsiella pneumoniae

2004
FRANCE
(TURKEY)
Poirel, Heritier, Tolün, Nordmann
AAC 2004 : 48: 15-22

NDM-1
Klebsiella pneumoniae

2009
SWEDEN
(INDIA)
Yong, Toleman, Giske, Cho, Sundman, Lee, Walsh
AAC 2009 : 53: 5046-5054

The carbapenemases in *Enterobacteriaceae*



* Aztreonam excluded

KPCs; Klebsiella Pneumoniae Carbapenemase

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2001, p. 1151–1161 Vol. 45, No. 4
0066-4804/01/$04.00+0 DOI: 10.1128/AAC.45.4.1151–1161.2001

Novel Carbapenem-Hydrolyzing β-Lactamase, KPC-1, from a Carbapenem-Resistant Strain of *Klebsiella pneumoniae*

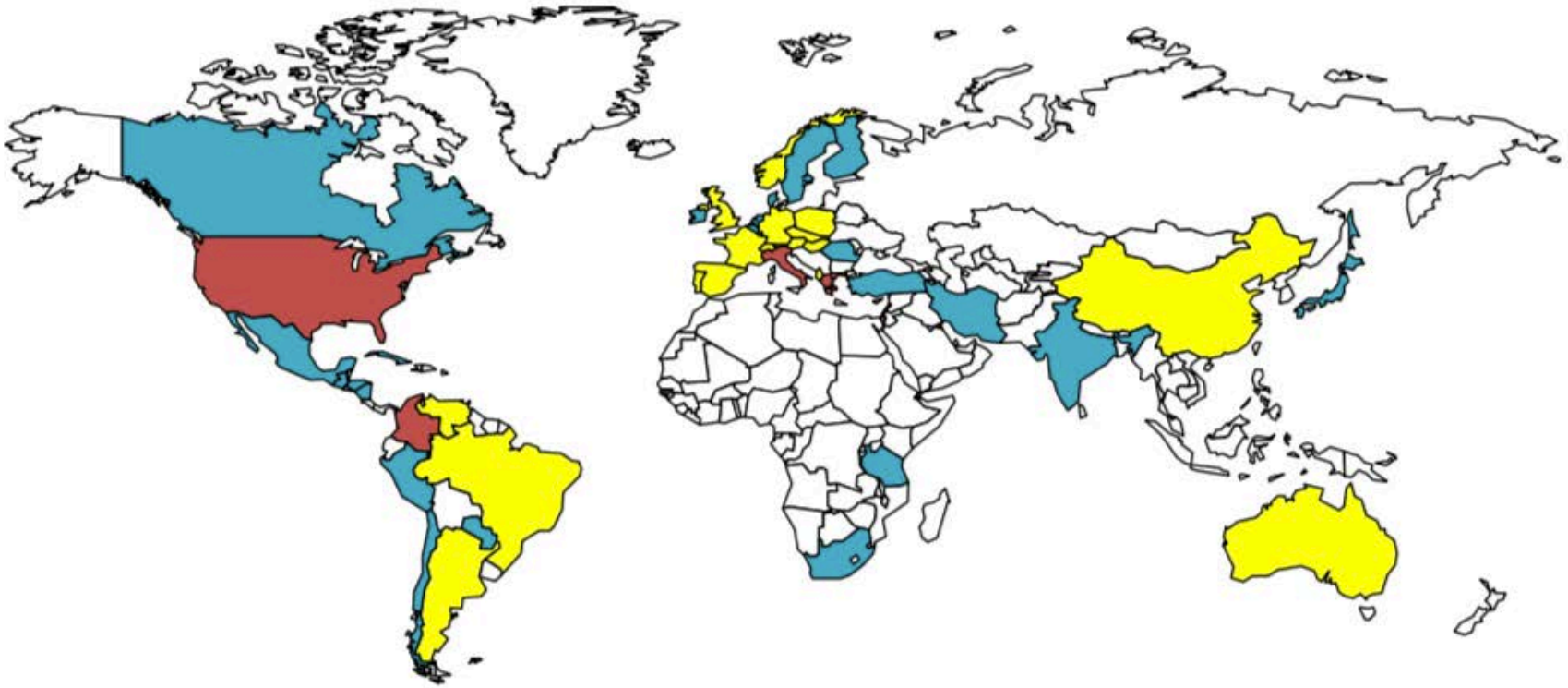
HESNA YIGIT,[1] ANNE MARIE QUEENAN,[2] GREGORY J. ANDERSON,[1] ANTONIO DOMENECH-SANCHEZ,[3] JAMES W. BIDDLE,[4] CHRISTINE D. STEWARD,[1] SEBASTIAN ALBERTI,[5] KAREN BUSH,[2] AND FRED C. TENOVER[1]*

Hospital Infections Program, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia 30333[1]; The R. W. Johnson Pharmaceutical Research Institute, Raritan, New Jersey 08869[2]; and Unidad de Investigacion, Hospital Son Dureta, Andreu Doria, Palma de Mallorca, 07014,[5] and Área de Microbiologia, Universidad de las Islas Baleares, Cra. Valldemosa, Palma de Mallorca, 07071,[3] Spain

Received 19 September 2000/Returned for modification 21 November 2000/Accepted 23 January 2001

Worldwide Epidemiology of Carbapenemase-producing *Enterobacteriaceae*

KPC producers



K. pneumoniae- hospitals

- Unknown
- Sporadic spread
- Outbreaks reported
- Endemicity

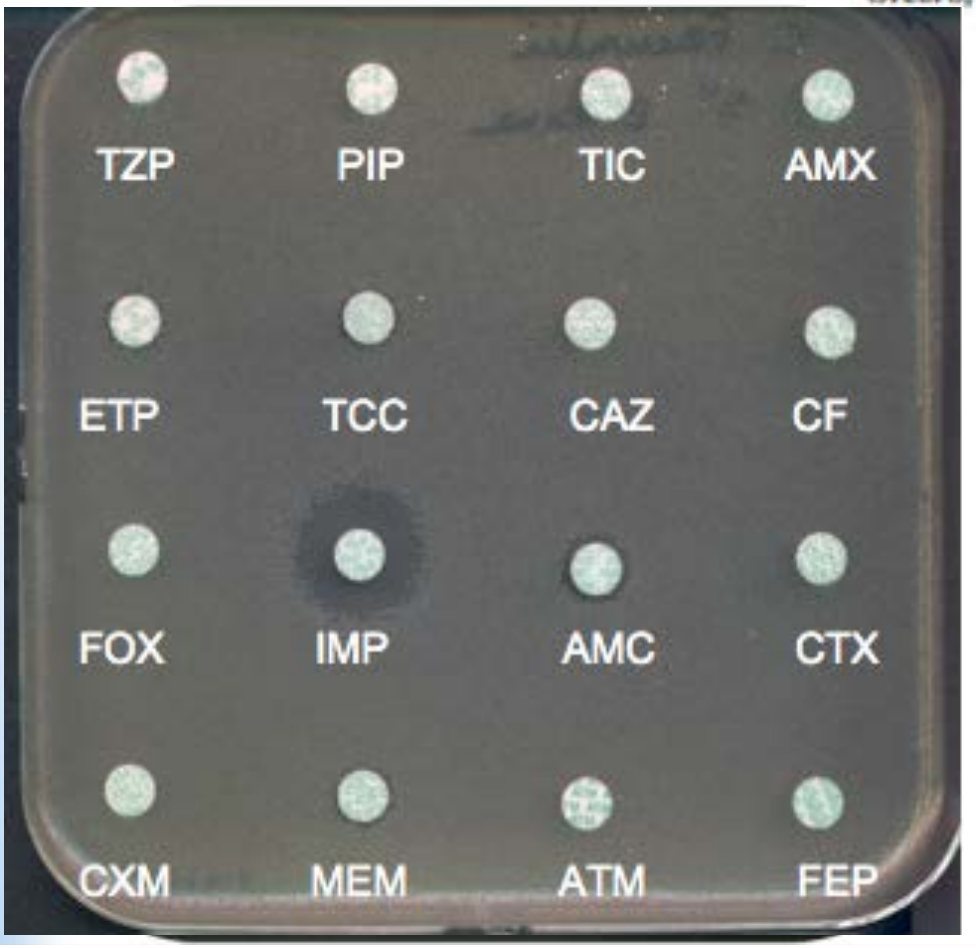
Bonomo et al., CID 2018;
Nordmann et al. EID 2015

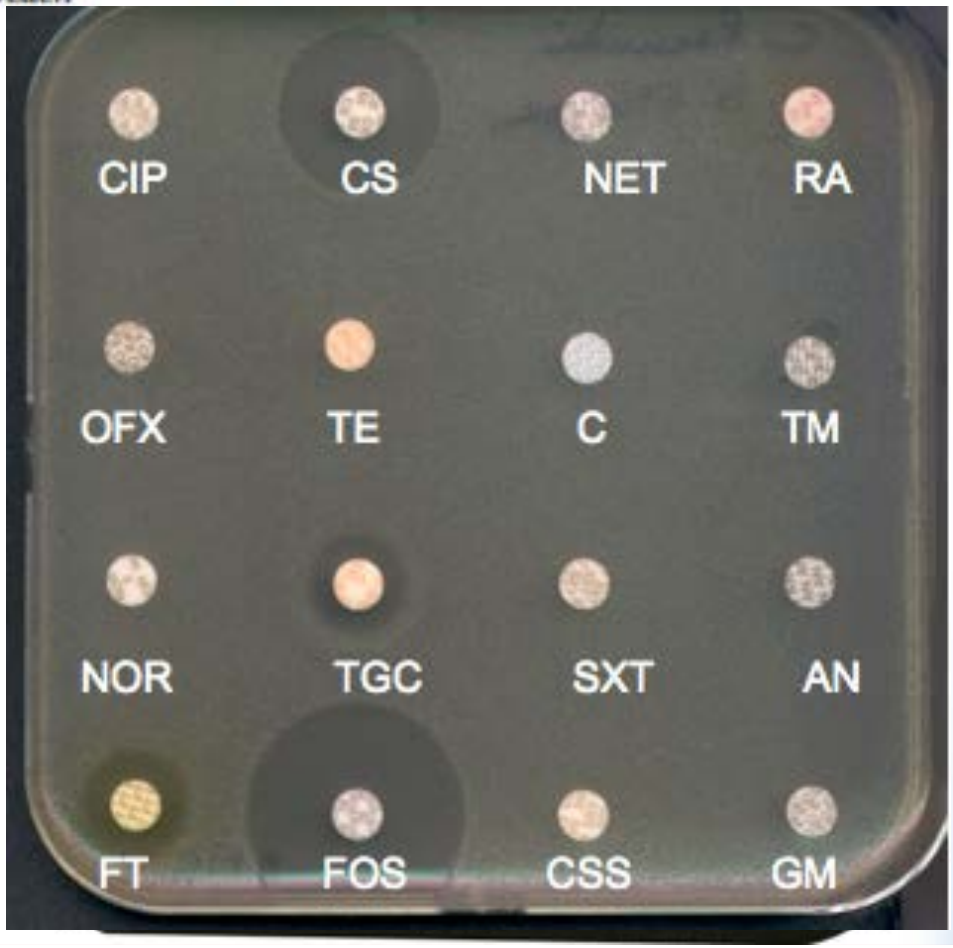
AAC,2009; 53 5046-5054

Characterization of a New Metallo-β-Lactamase Gene, *bla*$_{NDM-1}$, and a Novel Erythromycin Esterase Gene Carried on a Unique Genetic Structure in *Klebsiella pneumoniae* Sequence Type 14 from India[▽]

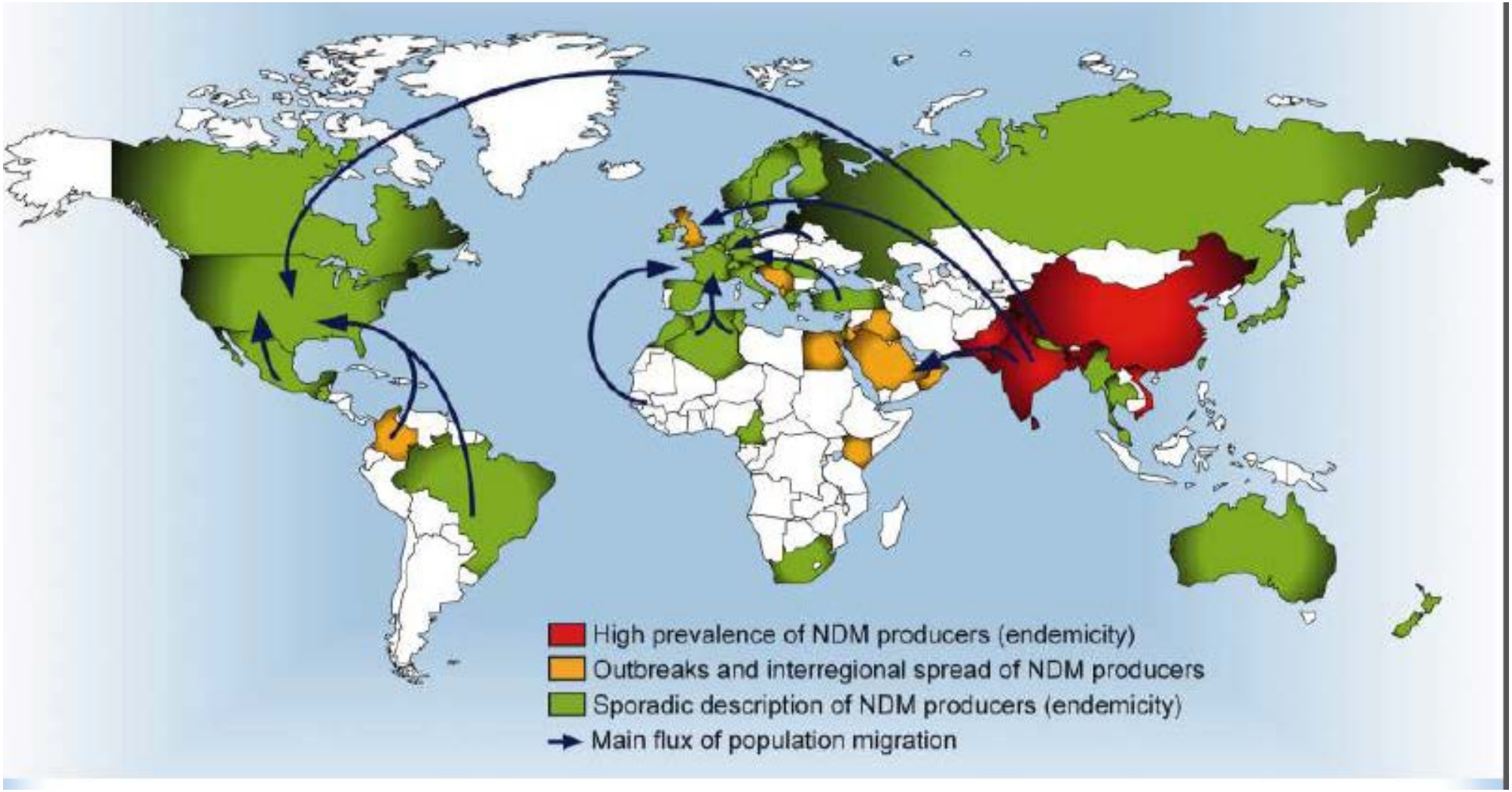
Dongeun Yong,[1,2] Mark A. Toleman,[2] Christian G. Giske,[3] Hyun S. Cho,[4] Kristina Sundman,[5] Kyungwon Lee,[1] and Timothy R. Walsh[2]*

Yonsei University College of Medicine, Research Institute of Antimicrobial Resistance, Seoul, Republic of Korea[1]; Department of Medical Microbiology, Cardiff University, Cardiff, United Kingdom[2]; Clinical Microbiology, MTC—Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden[3]; Yonsei University College of Life Science and Biotechnology, Seoul, Republic of Korea[4]; and Department of Clinical Microbiology, Örebro University Hospital, Örebro, Sweden[5]



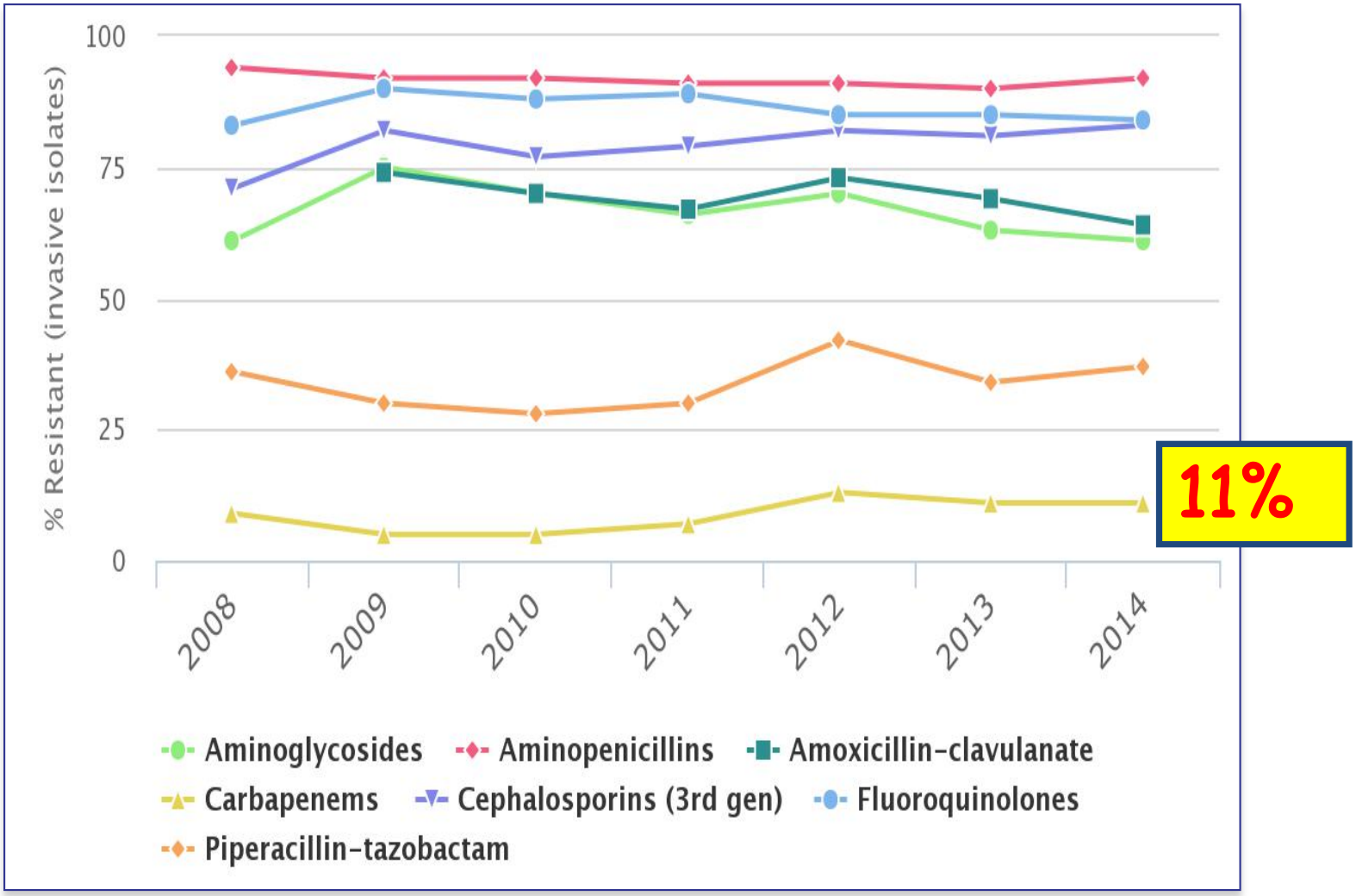


Wordwide spread of NDM carbapenemases in *Enterobacteriaceae*



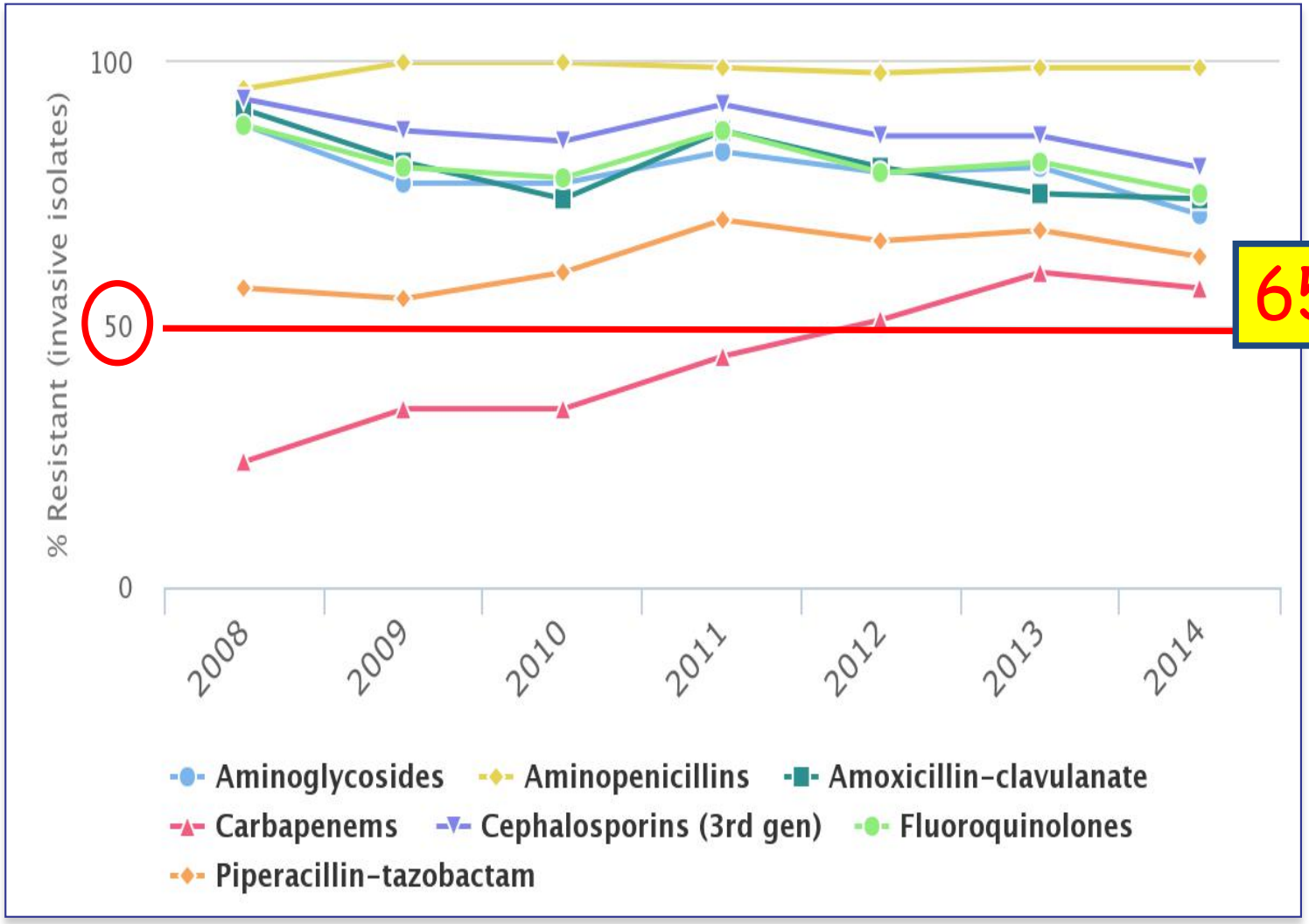
Nordmann et al EID 2015

Antibiotic resistance of *Escherichia coli* in India



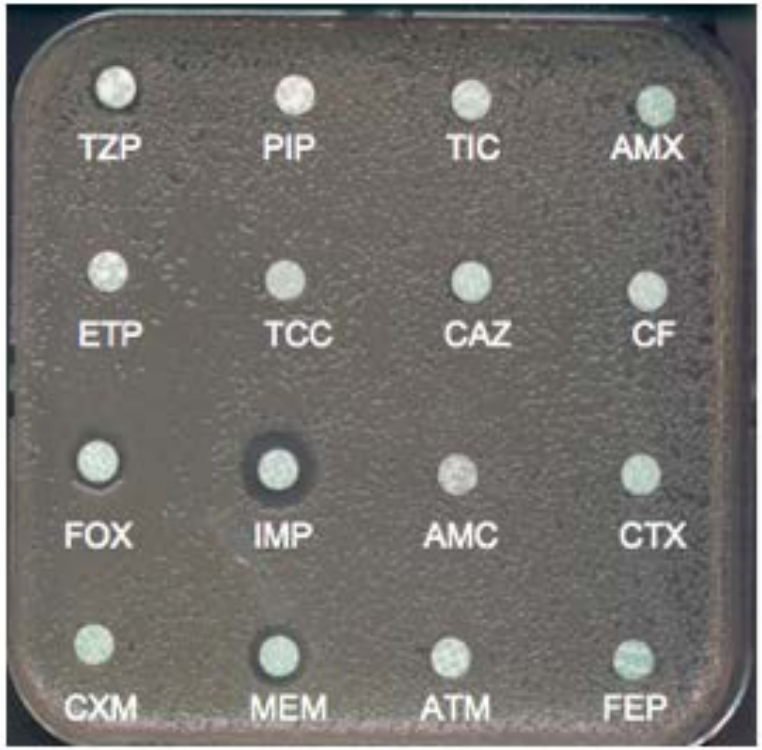
Center for Diseases Dynamics, Economics & Policy (cddep.org)

Antibiotic resistance of *Klebsiella pneumoniae* in India



Center for Diseases Dynamics, Economics & Policy (cddep.org)

OXA-48 + CTX-M-15

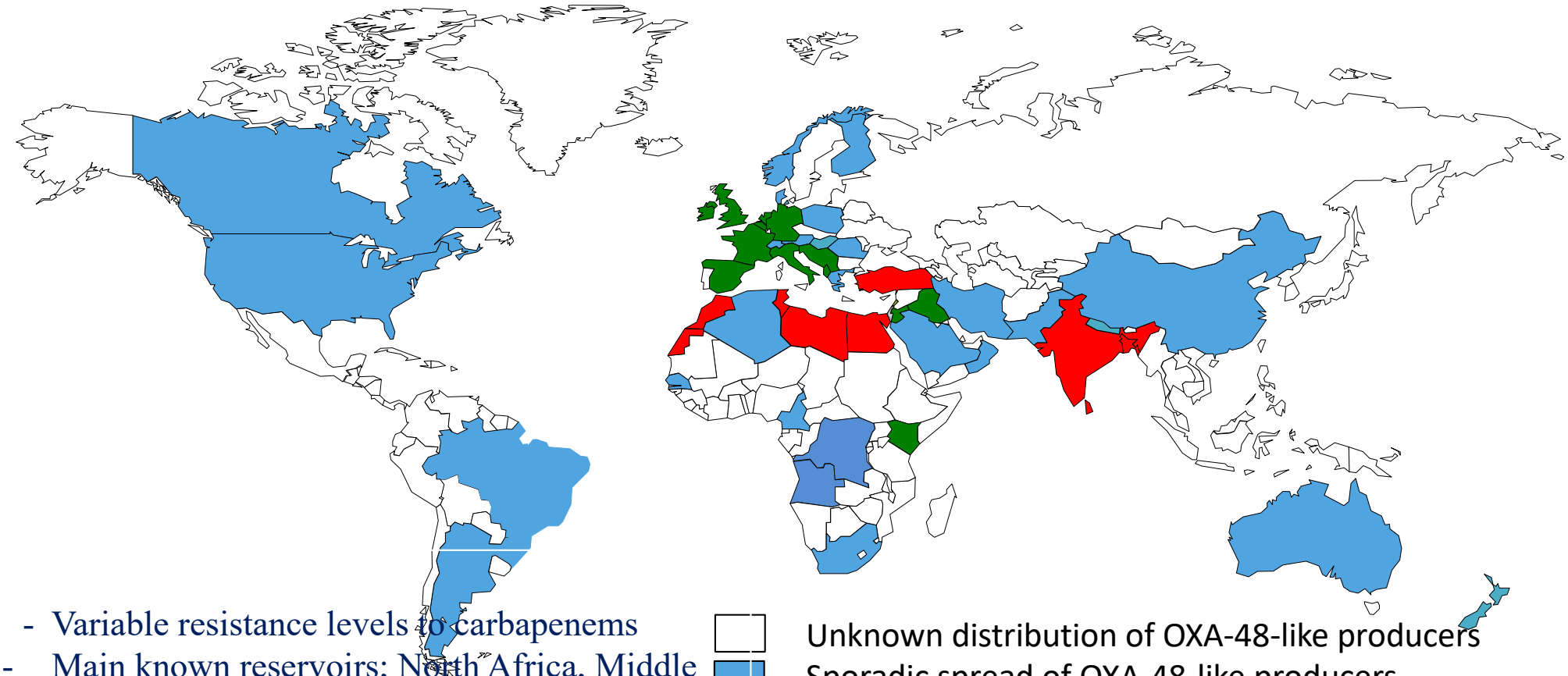


ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 2004, p. 15–22 Vol. 48, No. 1
0066-4804/04/$08.00+0 DOI: 10.1128/AAC.48.1.15–22.2004

Emergence of Oxacillinase-Mediated Resistance to Imipenem in *Klebsiella pneumoniae*

Laurent Poirel,[1] Claire Héritier,[1] Venus Tolün,[2] and Patrice Nordmann[1]*

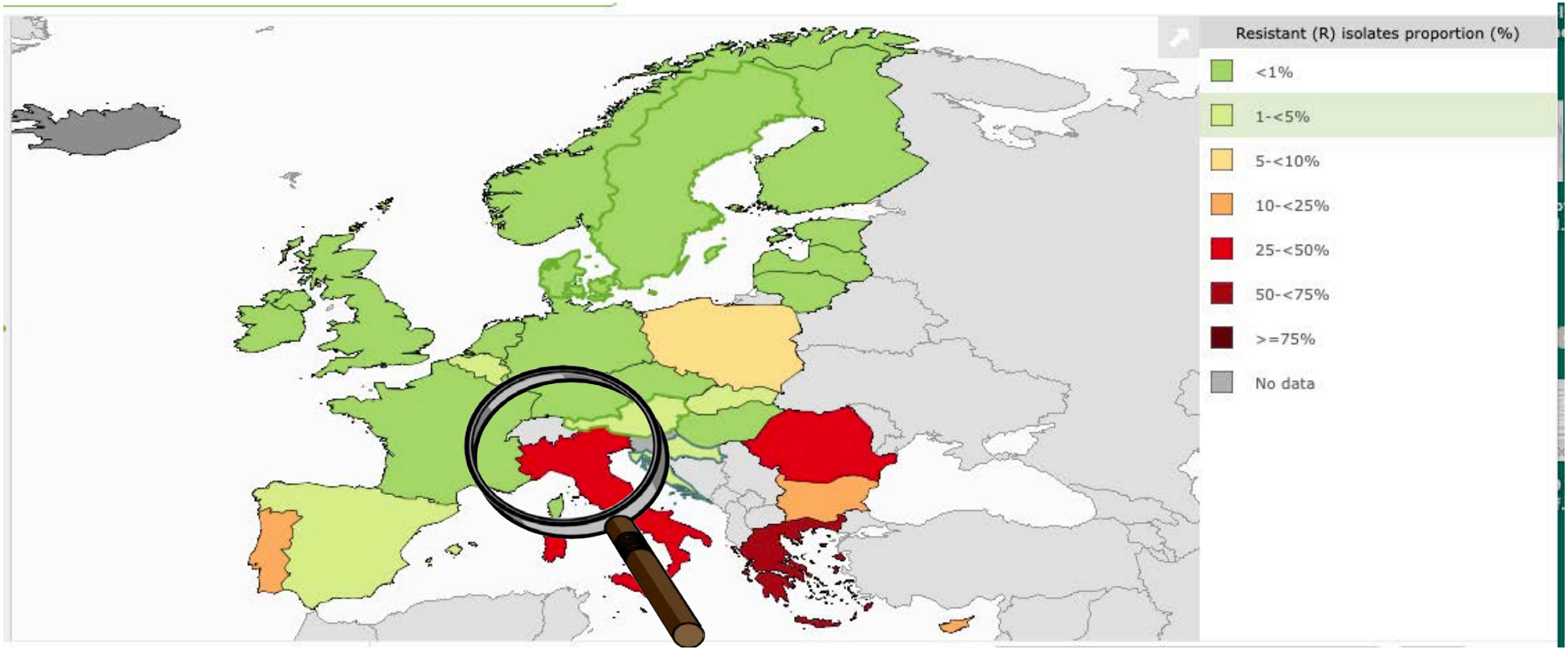
OXA-48-like producers- Enterobacterales, 2018



- Variable resistance levels to carbapenems
- Main known reservoirs; North Africa, Middle East, Turkey and India
- **Community aquisition(+++)** High frequency transfer
- *K. pneumoniae, E.cloacae,* ***E.coli*** *(++)*

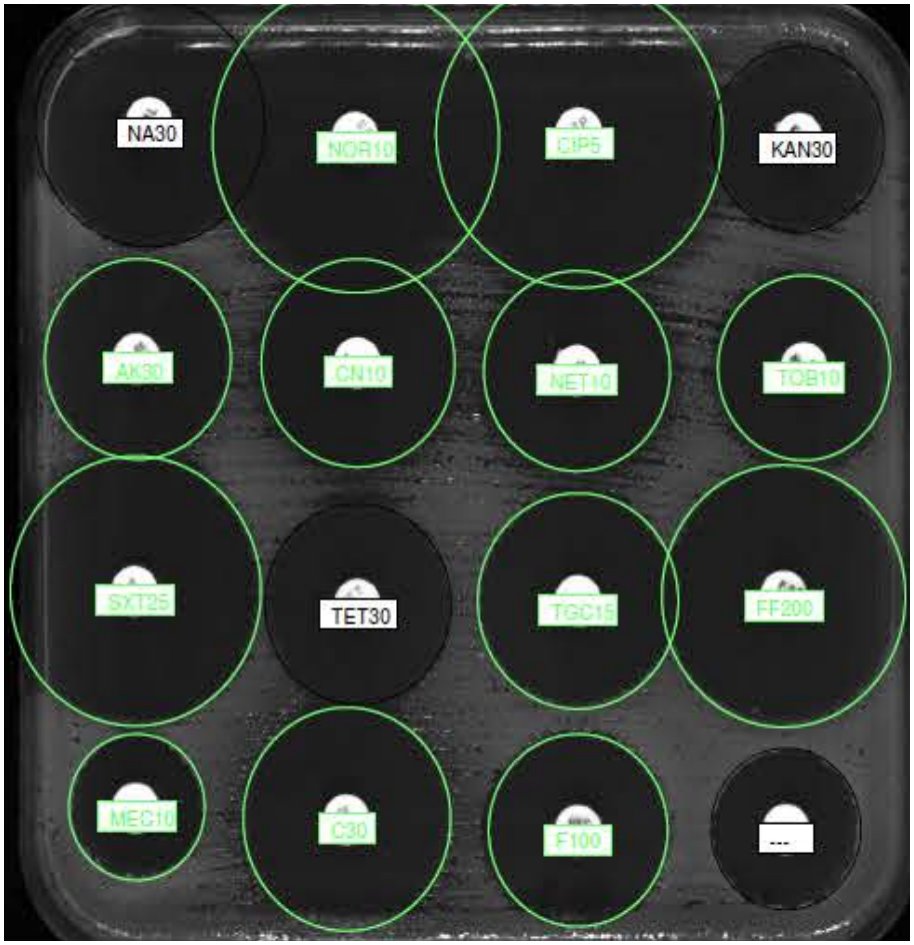
Unknown distribution of OXA-48-like producers
Sporadic spread of OXA-48-like producers
Outbreaks due to OXA-48-like producers
Endemicity of OXA-48-like producers

Adapted from Nordmann & Poirel, 2016 Clin Microb Infect,


Resistant (R) isolates proportion (%)
<1%
1-<5%
5-<10%
10-<25%
25-<50%
50-<75%
>=75%
No data


JE CROIS QU'ILS ONT DES PROBLÈMES, EN HELVÉTIE.
C'EST BIEN LEUR TOUR.
GAVLE
HELVETIE
?!

E. coli OXA-244 (OXA-48-like)

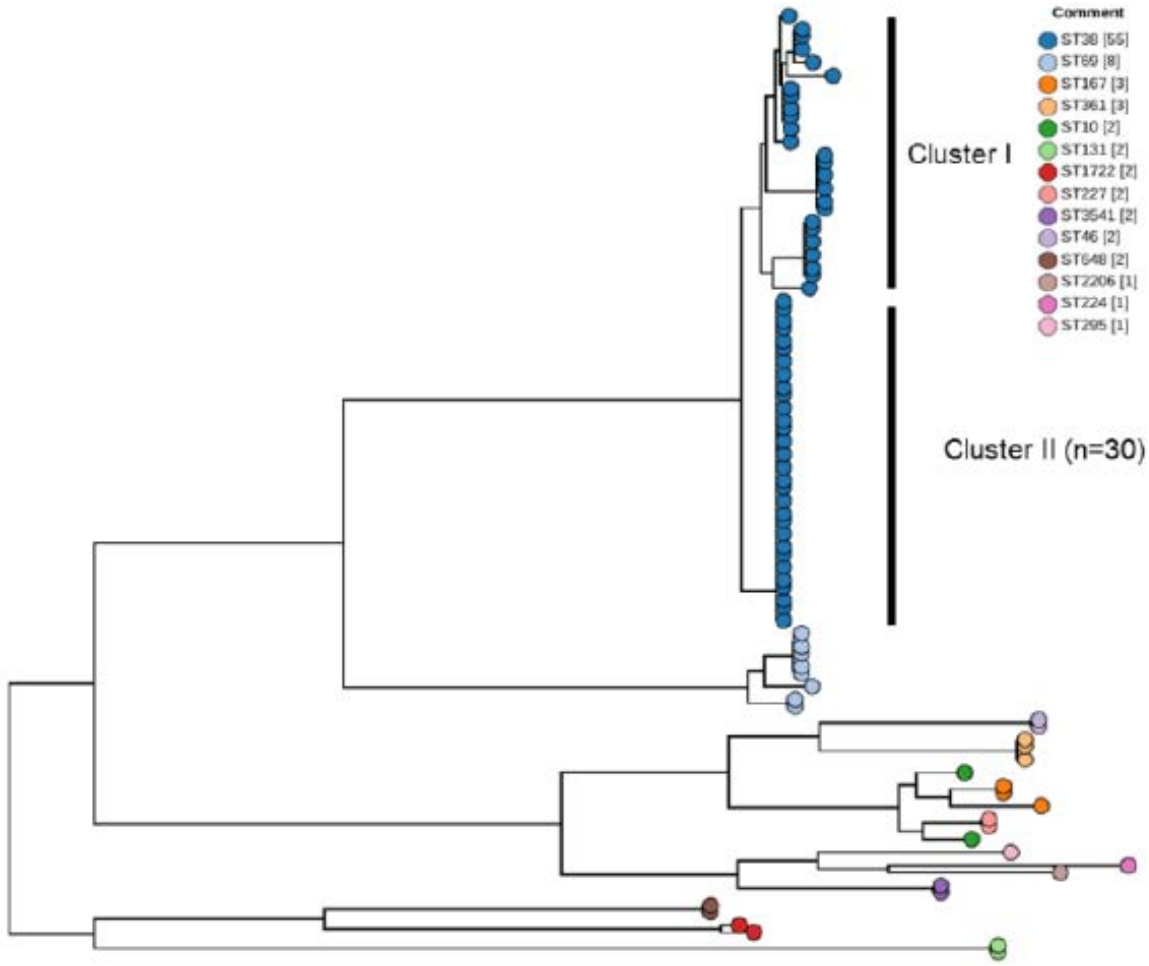


Ongoing dissemination of OXA-244 carbapenemase-producing *Escherichia coli* in Switzerland and their detection

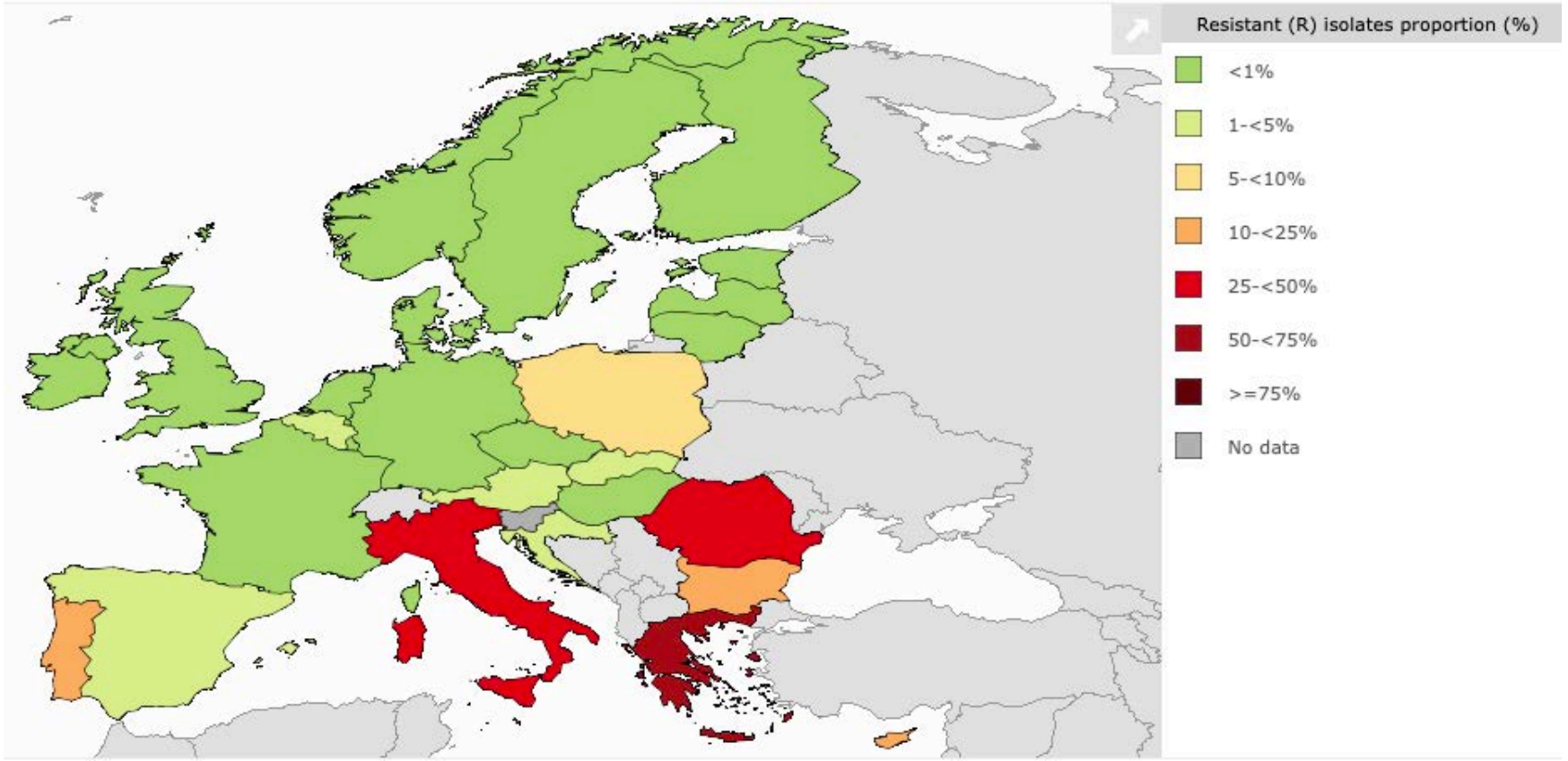
Amandine Masseron [a], Laurent Poirel [a,b,c,*], Linda Falgenhauer [d,e], Can Imirzalioglu [d], Julie Kessler [c], Trinad Chakraborty [d], Patrice Nordmann [a,b,c,e,f]

[a] Medical and Molecular Microbiology, Faculty of Science and Medicine, University of Fribourg, Switzerland
[b] INSERM European Unit (LEA), University of Fribourg, Switzerland
[c] Swiss National Reference Center for Emerging Antibiotic Resistance (NARA), University of Fribourg, Switzerland
[d] Institute of Medical Microbiology, and German Center for Infection Research (DZIF), Partner Site Giessen-Marburg-Langen, Justus Liebig University Giessen, Giessen, Germany
[e] Institute of Hygiene and Environmental Medicine, Justus Liebig University Giessen, Giessen, Germany

International spread of *E. coli* OXA-244 at least in Switzerland, Germany, France, UK, the Netherlands…



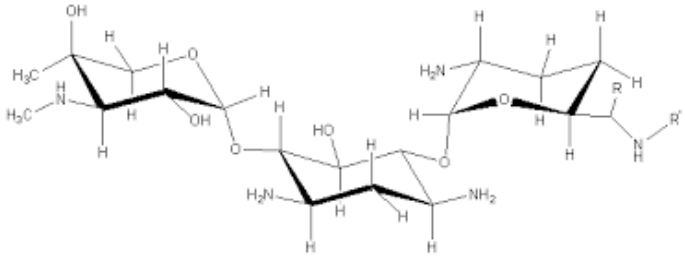
Carbapenem resistance *K. pneumoniae* Bacteremia. 2018



Carbapenemase producers are spreading now also in the community; NDM and OXA-48 like enzymes

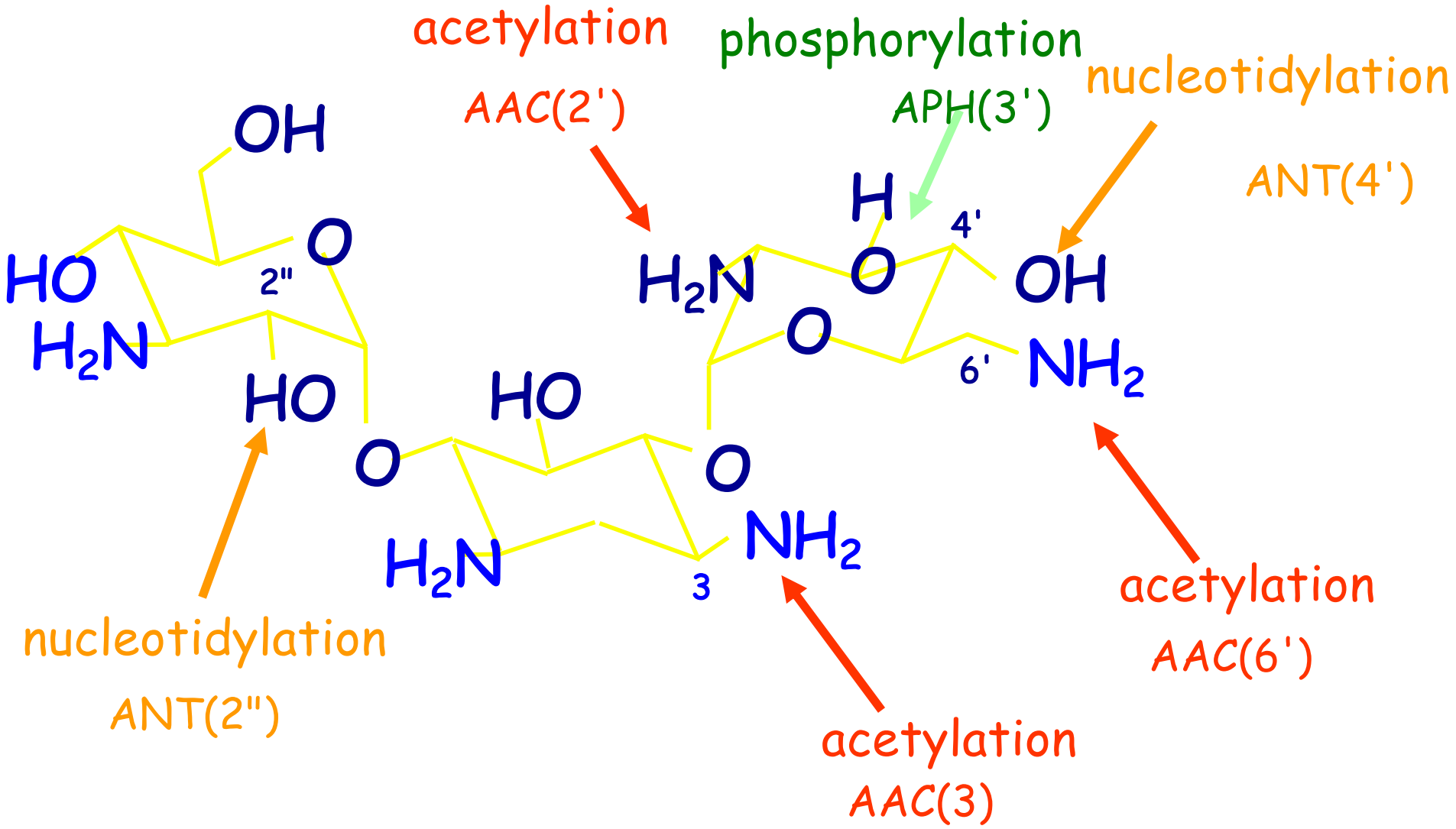
Important Emerging Resistances to Antibiotics

Aminoglycosides

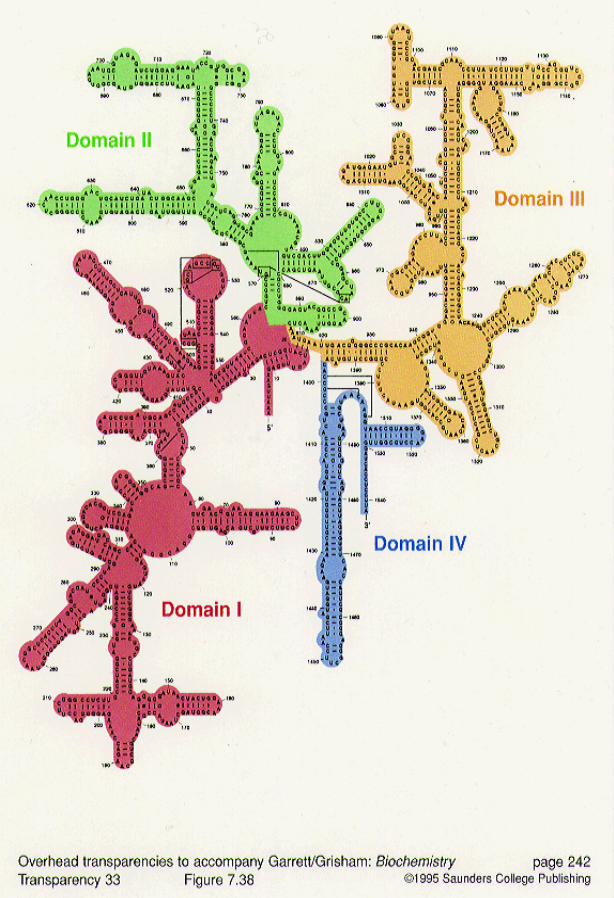


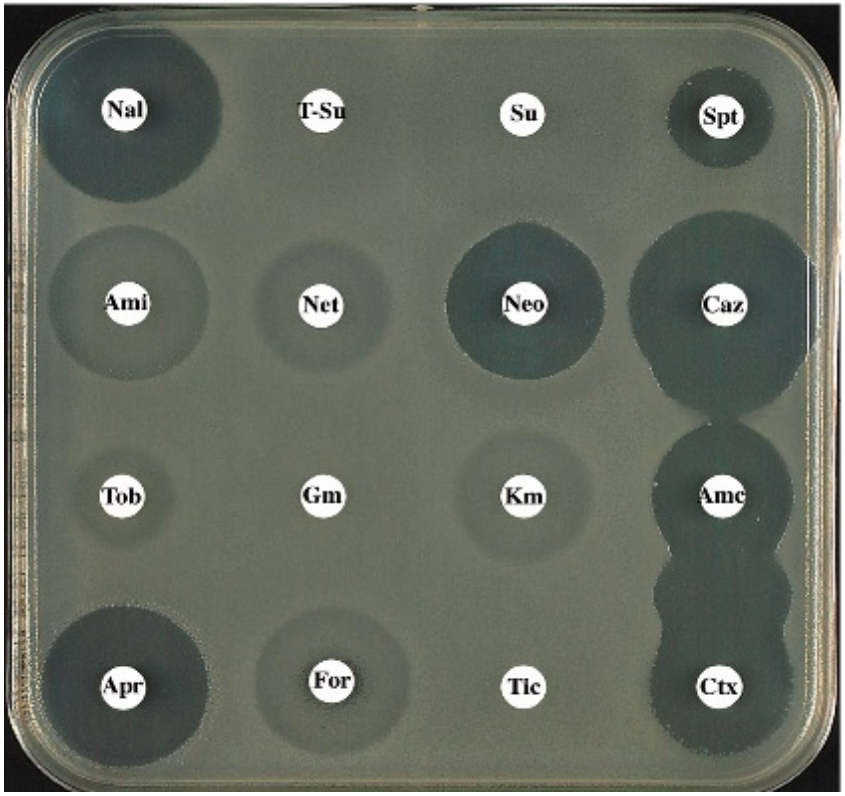
16S rRNA methylases

Main mechanisms of resistance to aminoglycosides

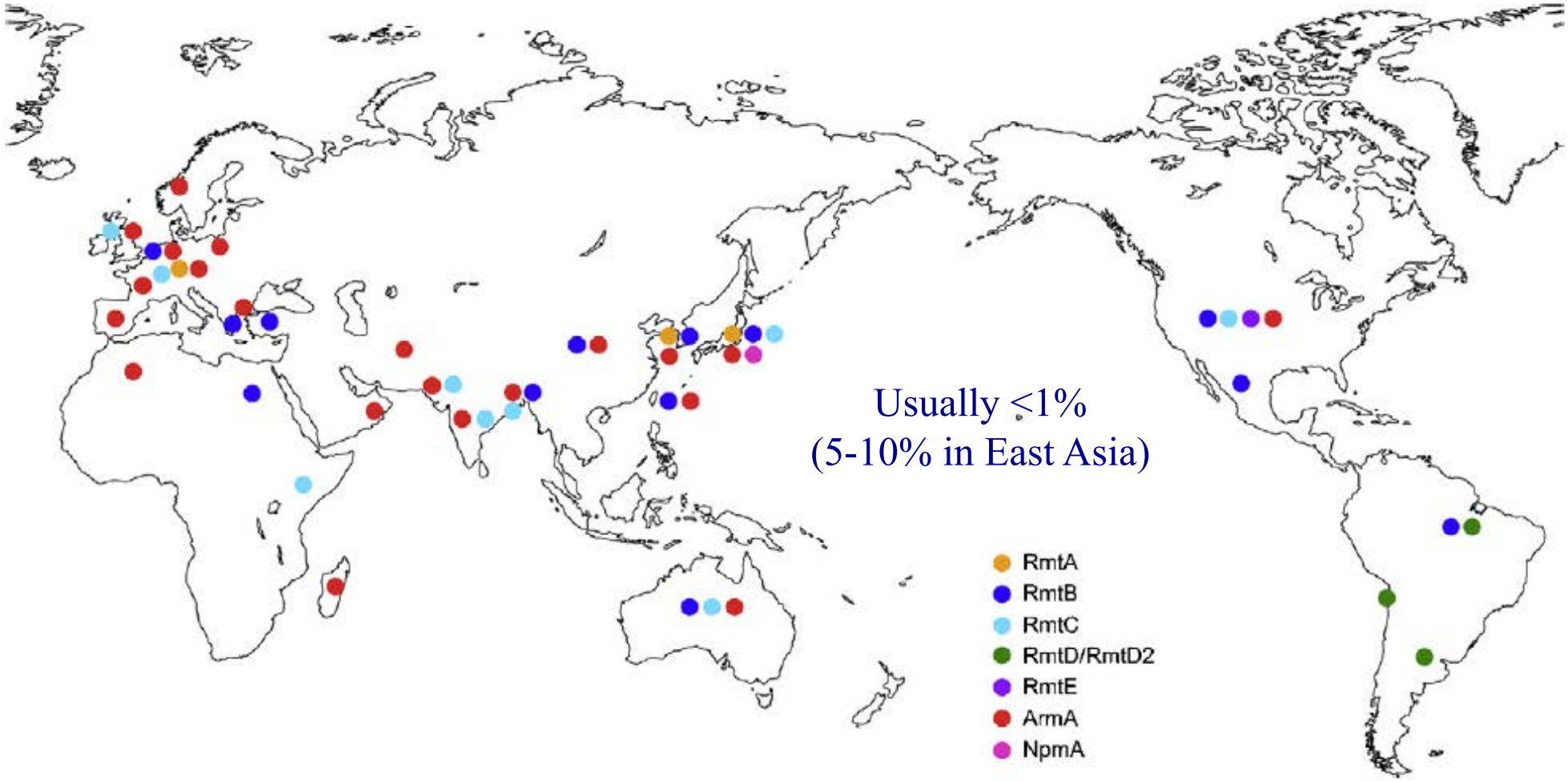


16s RNA methylase , RmtB in *K. pneumoniae*



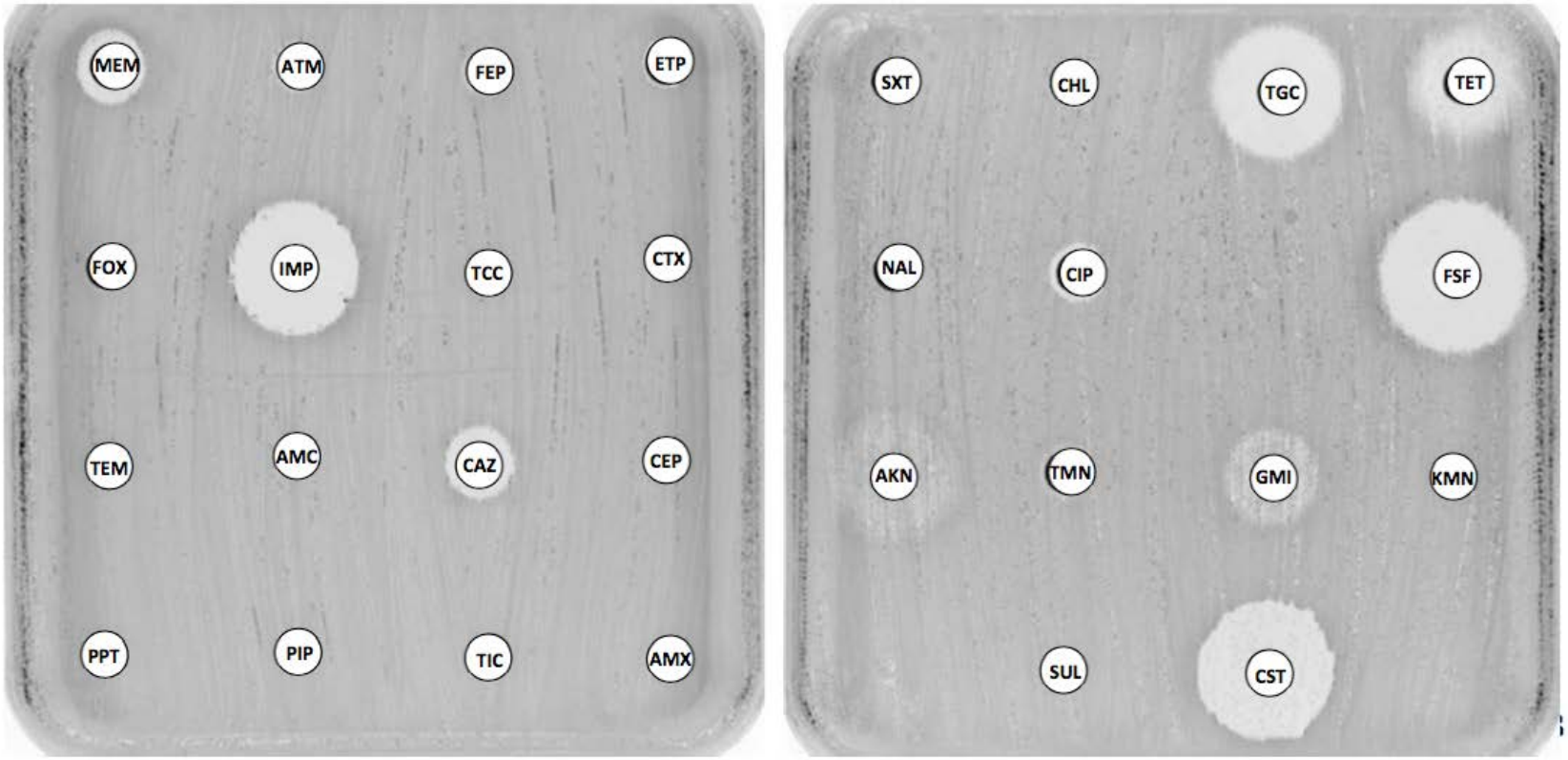


Prevalence / distribution of 16S rRNA methylases



Wachino & Arakawa, Drug Resist Updates 2012; 15:133-148

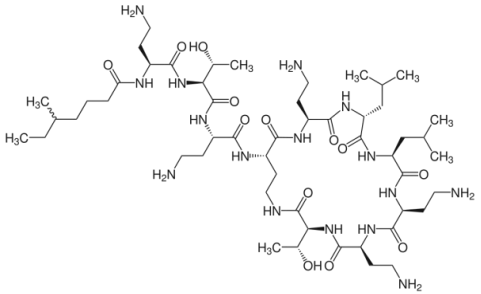
Multidrug-resistance *K. pneumoniae*



NDM-1 **RmtF**

Important Emerging Resistances to Antibiotics

Polymyxins



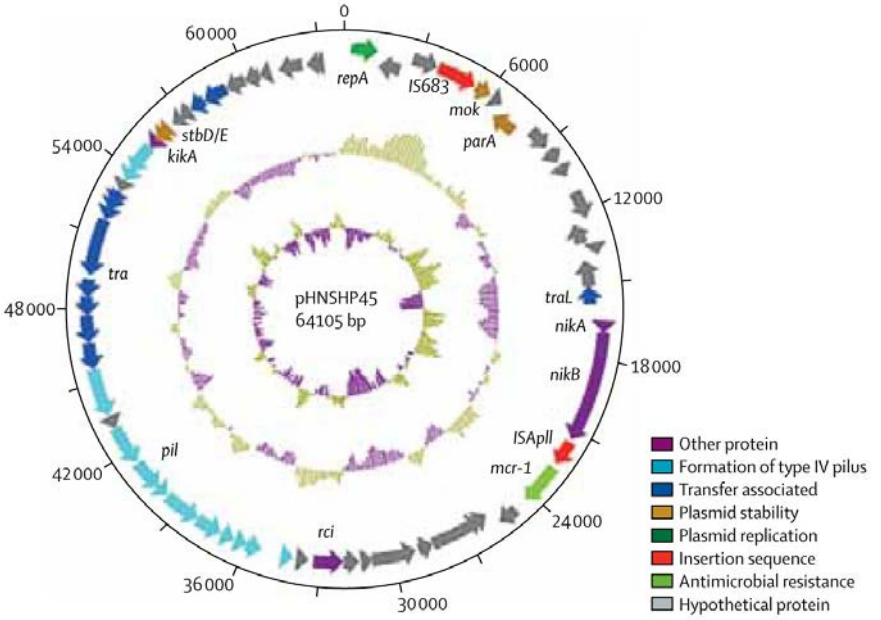
Resistance to polymyxins

Lancet Infect Dis, Nov 28, 2015

Plasmid-mediated resistance to colistin

Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study

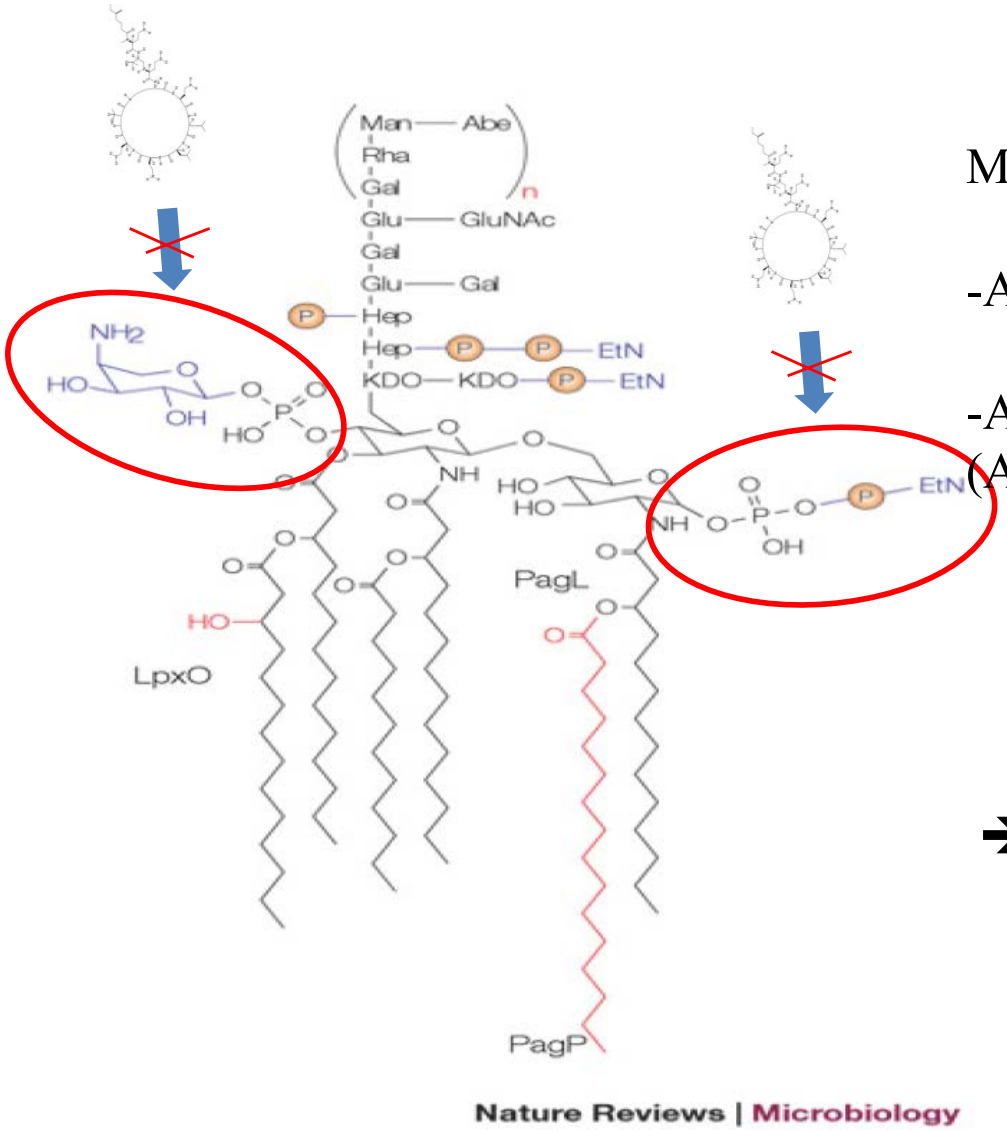
Yi-Yun Liu, Yang Wang*, Timothy R Walsh, Ling-Xian Yi, Rong Zhang, James Spencer, Yohei Doi, Guobao Tian, Baolei Dong, Xianhui Huang, Lin-Feng Yu, Danxia Gu, Hongwei Ren, Xiaojie Chen, Luchao Lv, Dandan He, Hongwei Zhou, Zisen Liang, Jian-Hua Liu, Jianzhong Shen*



	Year	Positive isolates (%)/number of isolates
Escherichia coli		
Pigs at slaughter	All	166 (20·6%)/804
Pigs at slaughter	2012	31 (14·4%)/216
Pigs at slaughter	2013	68 (25·4%)/268
Pigs at slaughter	2014	67 (20·9%)/320
Retail meat	All	78 (14·9%)/523
Chicken	2011	10 (4·9%)/206
Pork	2011	3 (6·3%)/48
Chicken	2013	4 (25·0%)/16
Pork	2013	11 (22·9%)/48
Chicken	2014	21 (28·0%)/75
Pork	2014	29 (22·3%)/130
Inpatient	2014	13 (1·4%)/902
Klebsiella pneumoniae		
Inpatient	2014	3 (0·7%)/420

Table 2: Prevalence of colistin resistance gene *mcr-1* by origin

Modification of the chemical structure of the LPS



Modifications :

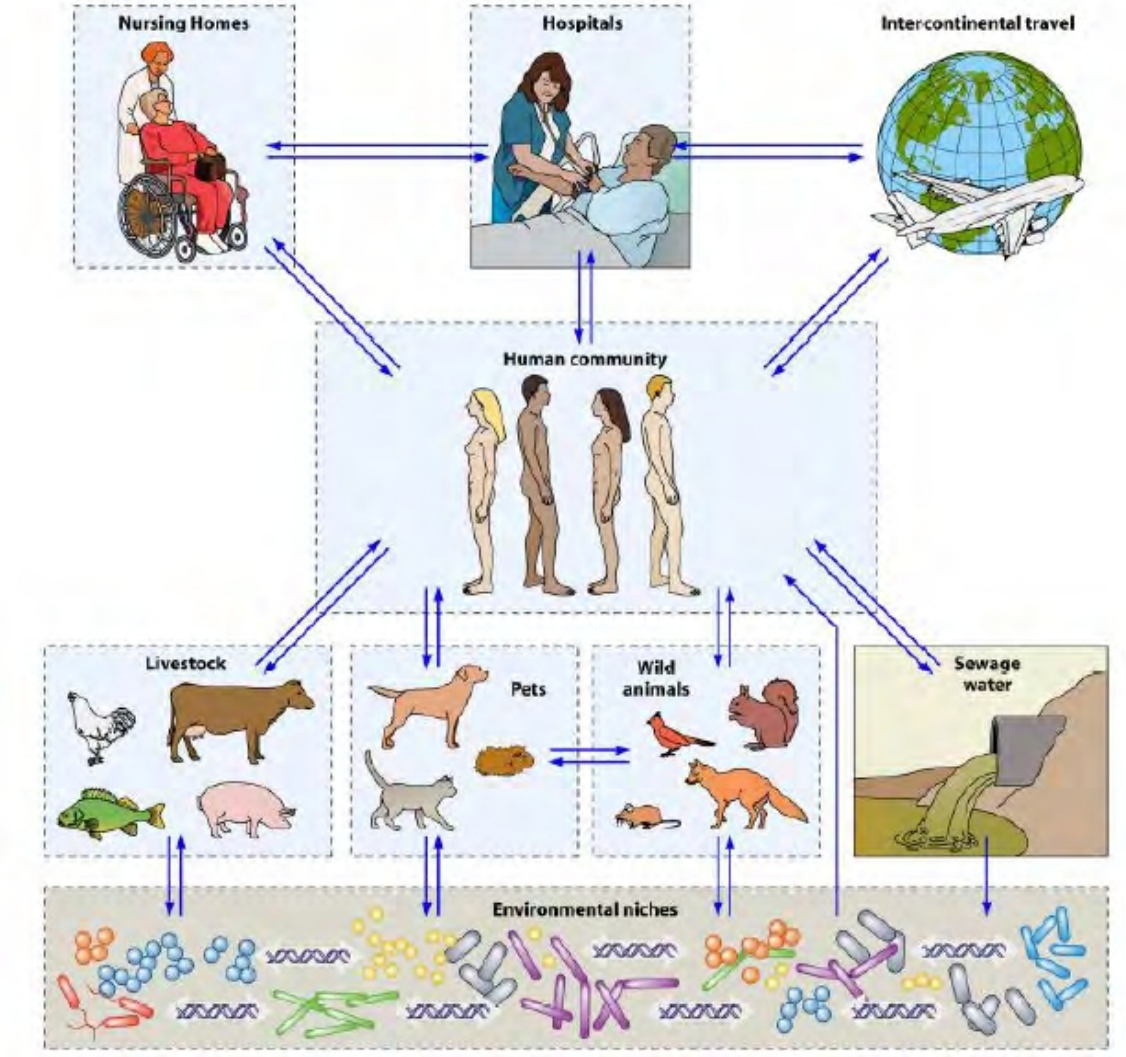
-Addition of phosphoethanolamine (pEtN)

-Addition of 4-amino-4-deoxyl-L-arabinose (Ara4N)

➔Adaptation against hostile environment

➔Lower affinity for cationic molecules such as colistin

A One-health world; plasmid-mediated colistin resistance (MCR)



… very rare in humans, in western Europe

Chromosome-encoded resistance to colistin

SURVEILLANCE AND OUTBREAK REPORT

National survey of colistin resistance among carbapenemase-producing *Enterobacteriaceae* and outbreak caused by colistin-resistant OXA-48-producing *Klebsiella pneumoniae*, France, 2014

A Jayol [1], L Poirel [1], L Dortet [2 3 4], P Nordmann [1 2 5]

1. Emerging Antibiotic Resistance Unit, Medical and Molecular Microbiology, Department of Medicine, University of Fribourg, Fribourg, Switzerland
2. Associated National Reference Centre for Antibiotic Resistance, Le Kremlin-Bicêtre, France
3. Faculty of Medicine, South-Paris University, Le Kremlin-Bicêtre, France
4. Bacteriology-Hygiene unit, Hospital Bicêtre, Assistance Publique /Hôpitaux de Paris, Le Kremlin-Bicêtre, France
5. University of Lausanne and University Hospital Center, Lausanne, Switzerland

Correspondence: Laurent Poirel (laurent.poirel@unifr.ch)

Citation style for this article:
Jayol A, Poirel L, Dortet L, Nordmann P. National survey of colistin resistance among carbapenemase-producing Enterobacteriaceae and outbreak caused by colistin-resistant OXA-48-producing Klebsiella pneumoniae, France, 2014. Euro Surveill. 2016;21(37):pii=30339. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.37.30339

Article submitted on 30 October 2015 / accepted on 04 April 2016 / published on 15 September 2016

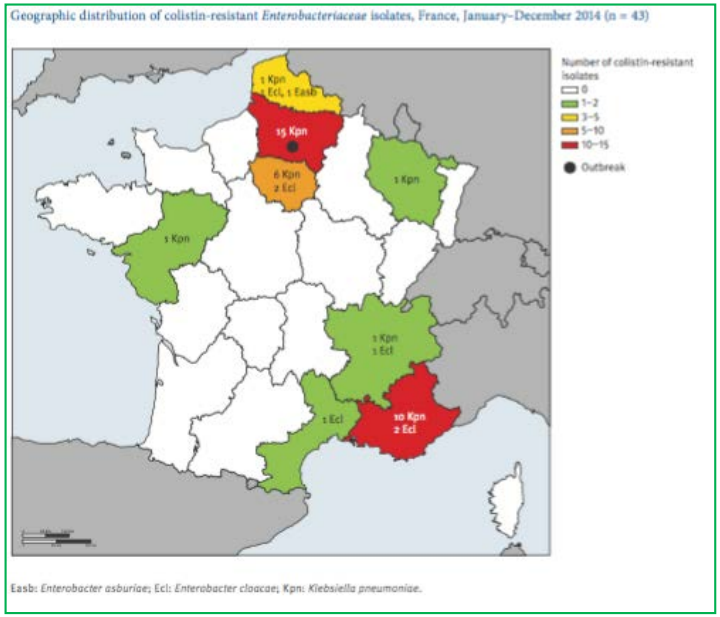
From January 2014 to December 2014, 972 consecutive non-replicate carbapenemase-producing *Enterobacteriaceae* isolates from colonised or infected patients were collected at the Associated French National Reference Centre as part of the French national survey on antimicrobial resistance. It included 577 *Klebsiella* spp. (59%), 236 *Escherichia coli* (24%), 108 *Enterobacter* spp. (11%), 50 *Citrobacter* spp. (5%), and a single *Salmonella* spp. isolate (0.1%). Of 561 *K. pneumoniae* isolates, 35 were found to be resistant to colistin (6.2%). PFGE analysis revealed a clonal outbreak involving 15 *K. pneumoniae* isolates belonging to sequence type ST11, recovered in a single hospital in the Picardie region in northern France. Those clonally related isolates showed variable levels of resistance to colistin, ranging from 4 to 64 mg/L. They harboured the bla_{OXA-48} carbapenemase gene and the $bla_{CTX-M-15}$ extended-spectrum beta-lactamase gene. Among the 91 *Enterobacter cloacae* isolates, seven were resistant to colistin and produced different types of carbapenemases. Surprisingly, none of the *E. coli* and *Citrobacter* spp. isolates showed resistance to colistin. This national survey including carbapenemase-producing isolates recovered in 2014 reported a high rate of colistin resistance in *K. pneumoniae* and *E. cloacae* (6.2% and 7.7%, respectively) in France.

currently almost unknown in most parts of the world. In Italy, an increase in carbapenemase-producing *Enterobacteriaceae* has been noted in the past years, but the situation remains unknown in France [1]. The lack of information about the prevalence of colistin resistance among multidrug-resistant enterobacterial isolates derives from several reasons: (i) so far, there has been limited interest in that field, (ii) methods used for determination of colistin susceptibility are not adequate, and (iii) the lack of well-defined breakpoints does not allow precise determination of prevalence. However, the recent identification of a plasmid-borne polymyxin resistance determinant (MCR-1) raised a very serious concern in that resistance to colistin might widely disseminate [2].

The aim of this study was to evaluate retrospectively the prevalence of colistin resistance among a collection of CPE strains recovered in France during a period of one year and to analyse the phenotypic, genotypic features and clonality of the colistin-resistant isolates.

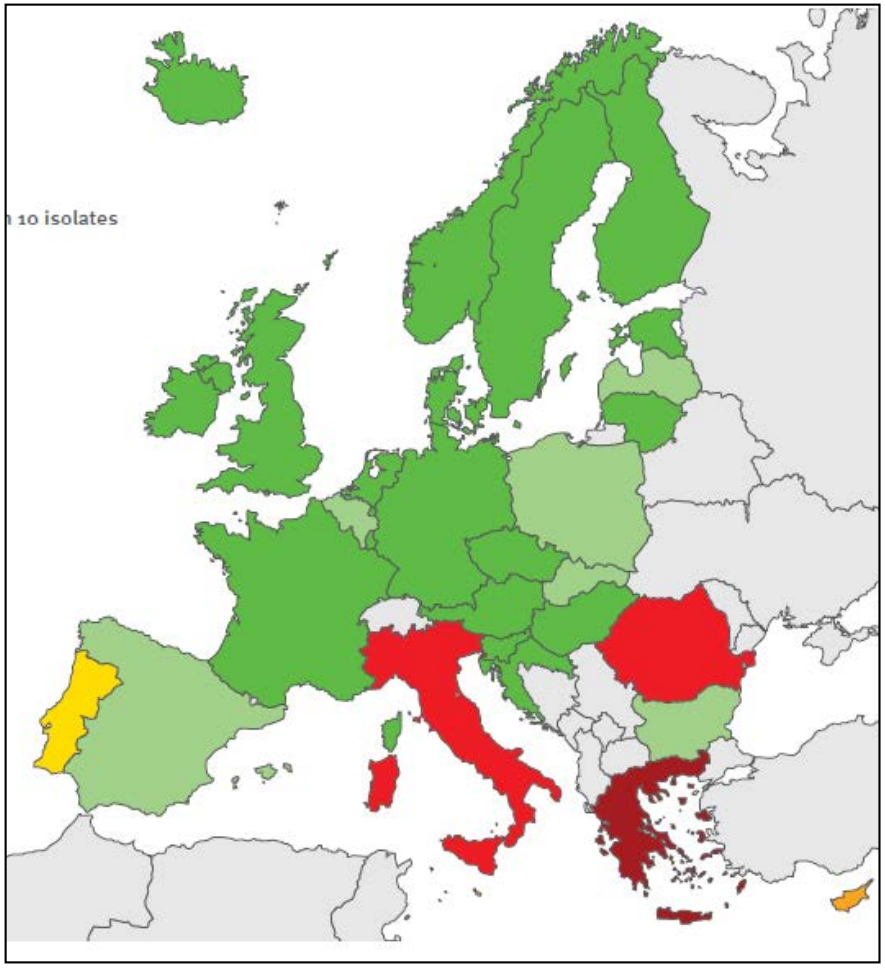
Methods

Carbapenemase-producing *Enterobacteriaceae* isolates

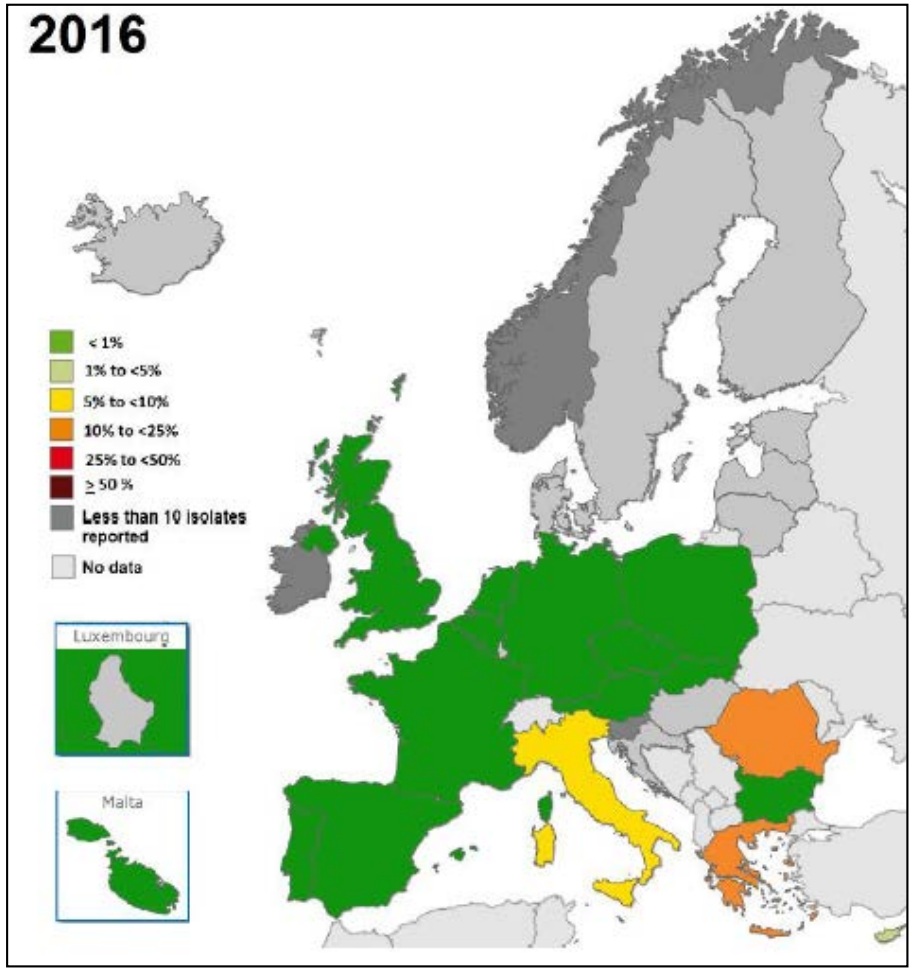


Klebsiella pneumoniae : resistance to carbapenems and colistin

Carbapenem-R



Carbapenem+colistin-R



EARS-Net surveillance data, November 2017

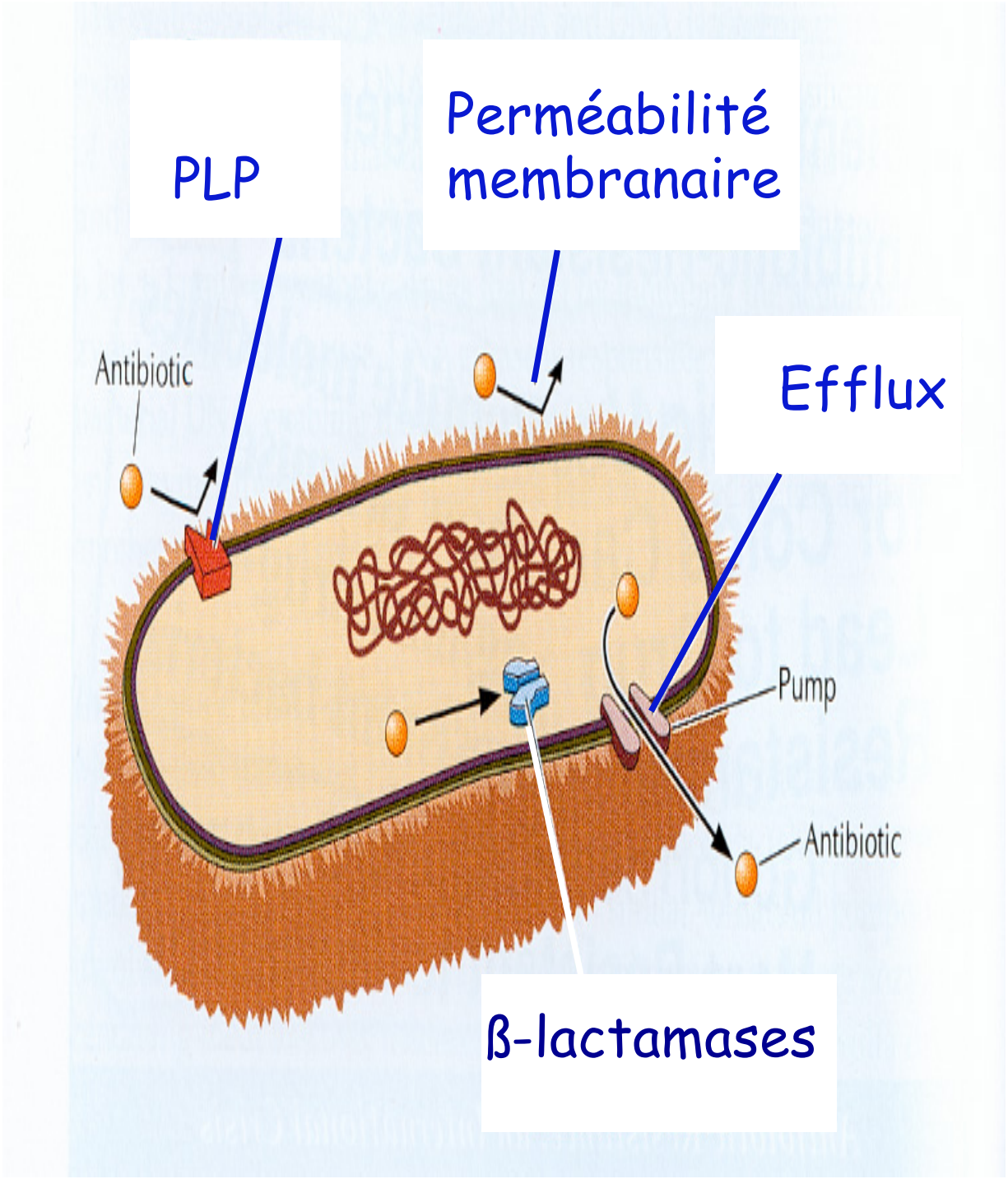
Pseudomonas aeruginosa

P. aeruginosa

- Faible perméabilité membranaire (100 fois moindre que celle de *E. coli* pour la céfalotine)

• Systèmes d'efflux constitutifs : au moins une douzaine...

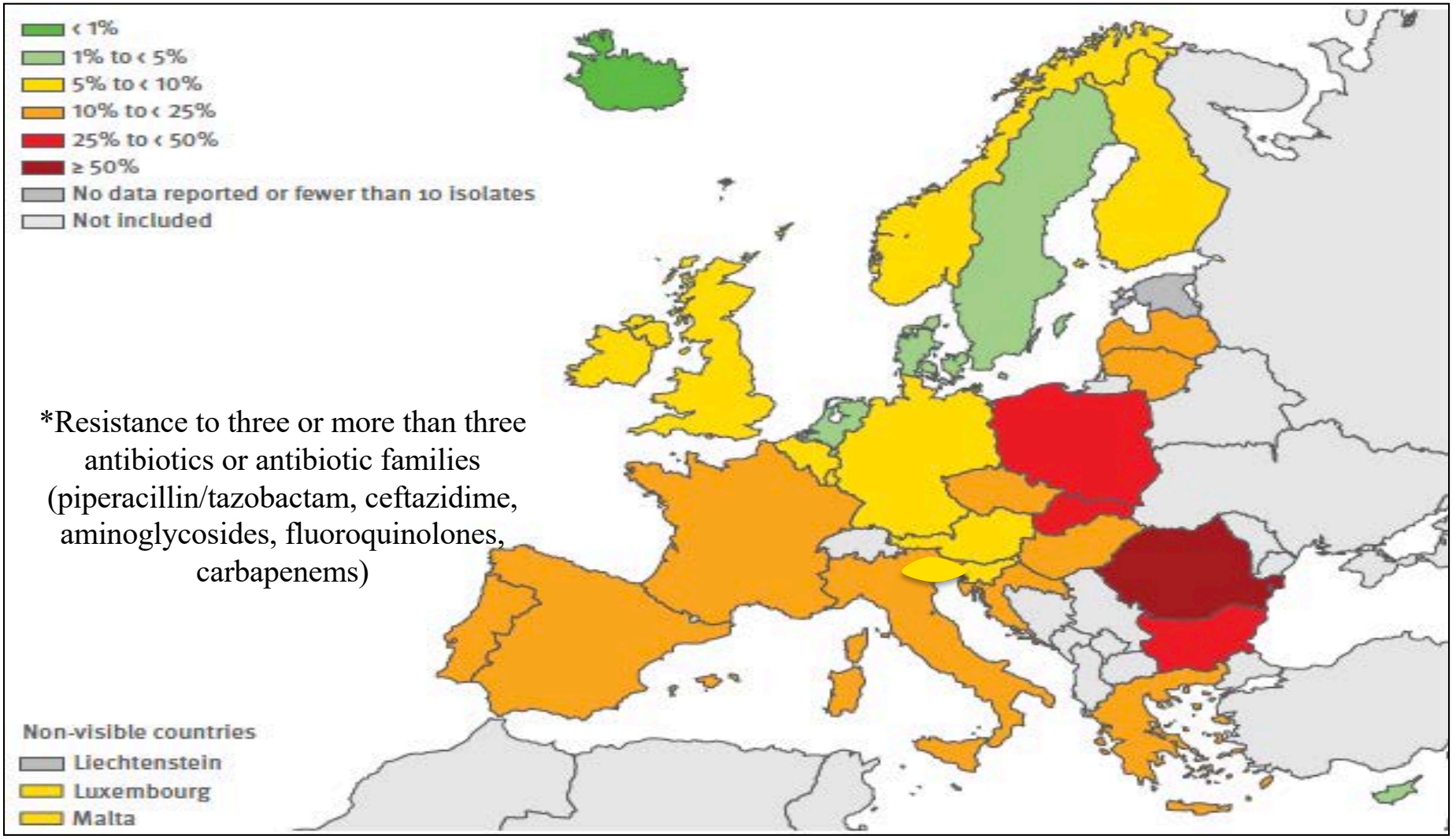
• Expression d'une céphalosporinase naturelle (AmpC) chromosomique et inductible



Major concerns with ß-lactam resistance

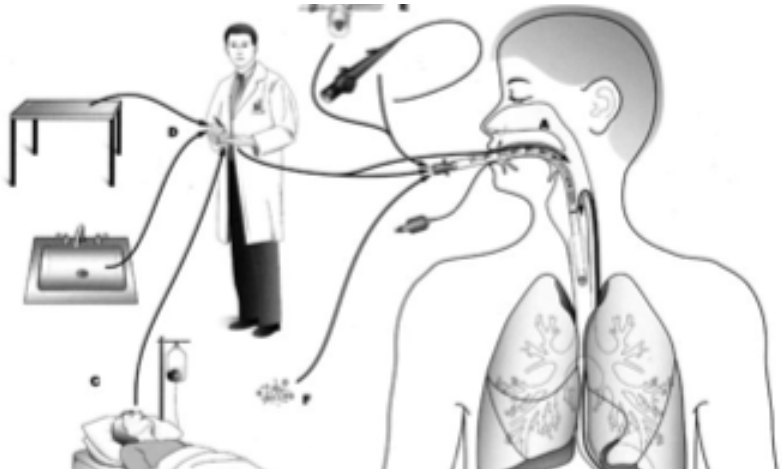
	Cephalosporins	Carbapenems
	- Ceftazidime - Cefepime	- Imipenem - Meropenem
A. baumannii	**AmpC ↑ +++** ESBLs +	**Carbapenemases +++**
P. aeruginosa	**AmpC ↑ +++** ESBLs + Carbapenemases +	**OprD ↓ +++** Carbapenemases +

Multiresistance* in *P. aeruginosa* (2015)



http://atlas.ecdc.europa.eu/public/index.aspx?Instance=GeneralAtlas

Acinetobacter baumannii



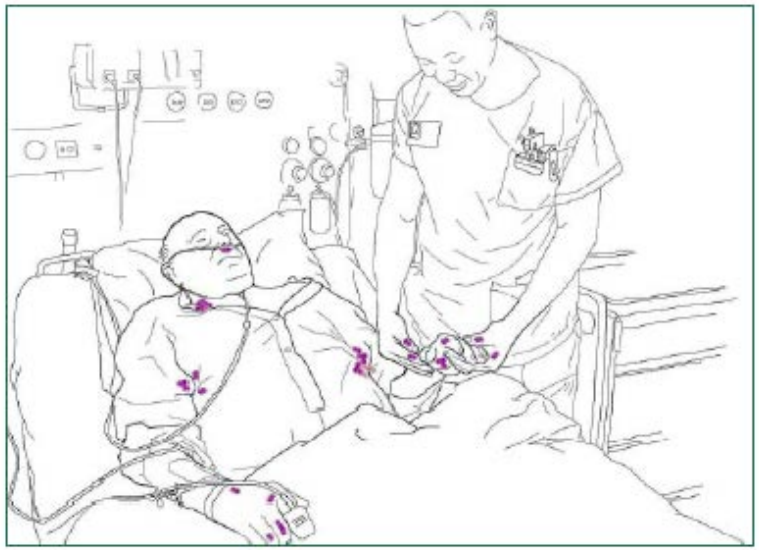
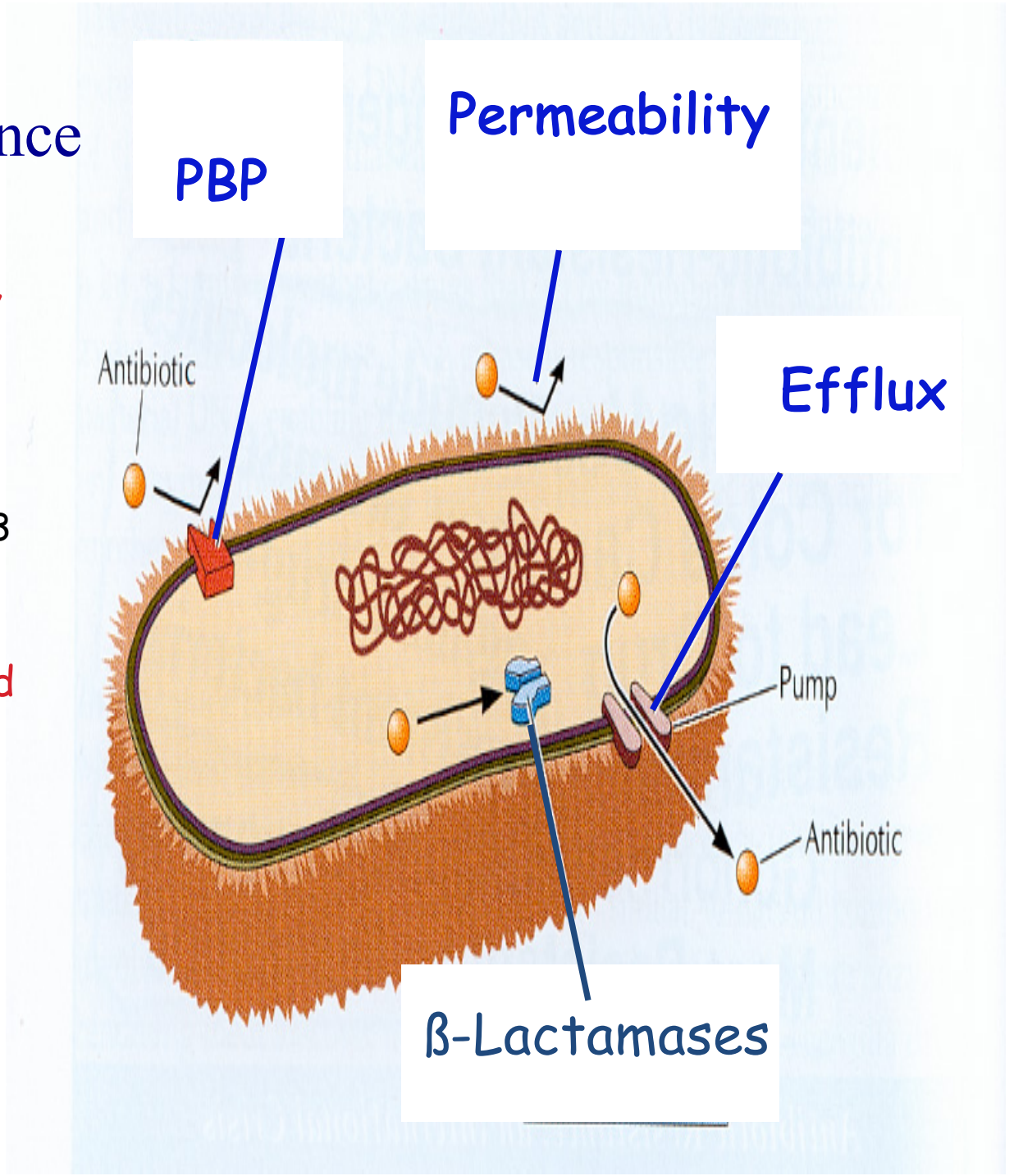


Figure 2: Organism transfer from patient to health-care worker's hands
Contact between the health-care worker and the patient results in cross-transmission of microorganisms. In this case, Gram-positive cocci from the patient's own flora.

The secrets of a successful resistance

- Low membrane permeability (3% that of *E. coli* for cefalotin)
- Constitutive efflux systems : 3 described AdeABC...
- Expression of naturally- and chromosomally- occurring ß-lactamases

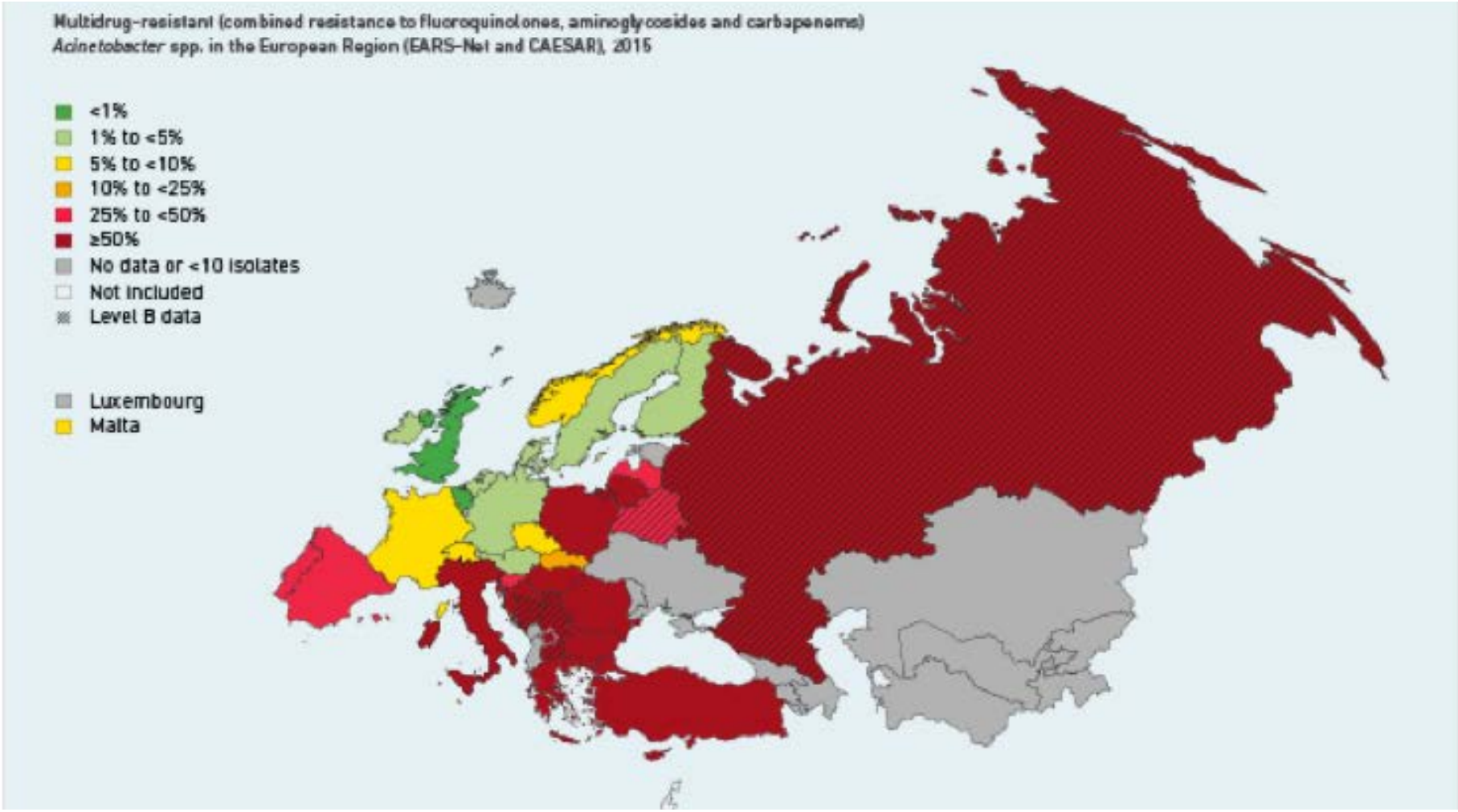
- cephalosporinase (AmpC)
- oxacillinase (OXA-51)



Major concerns with ß-lactam resistance

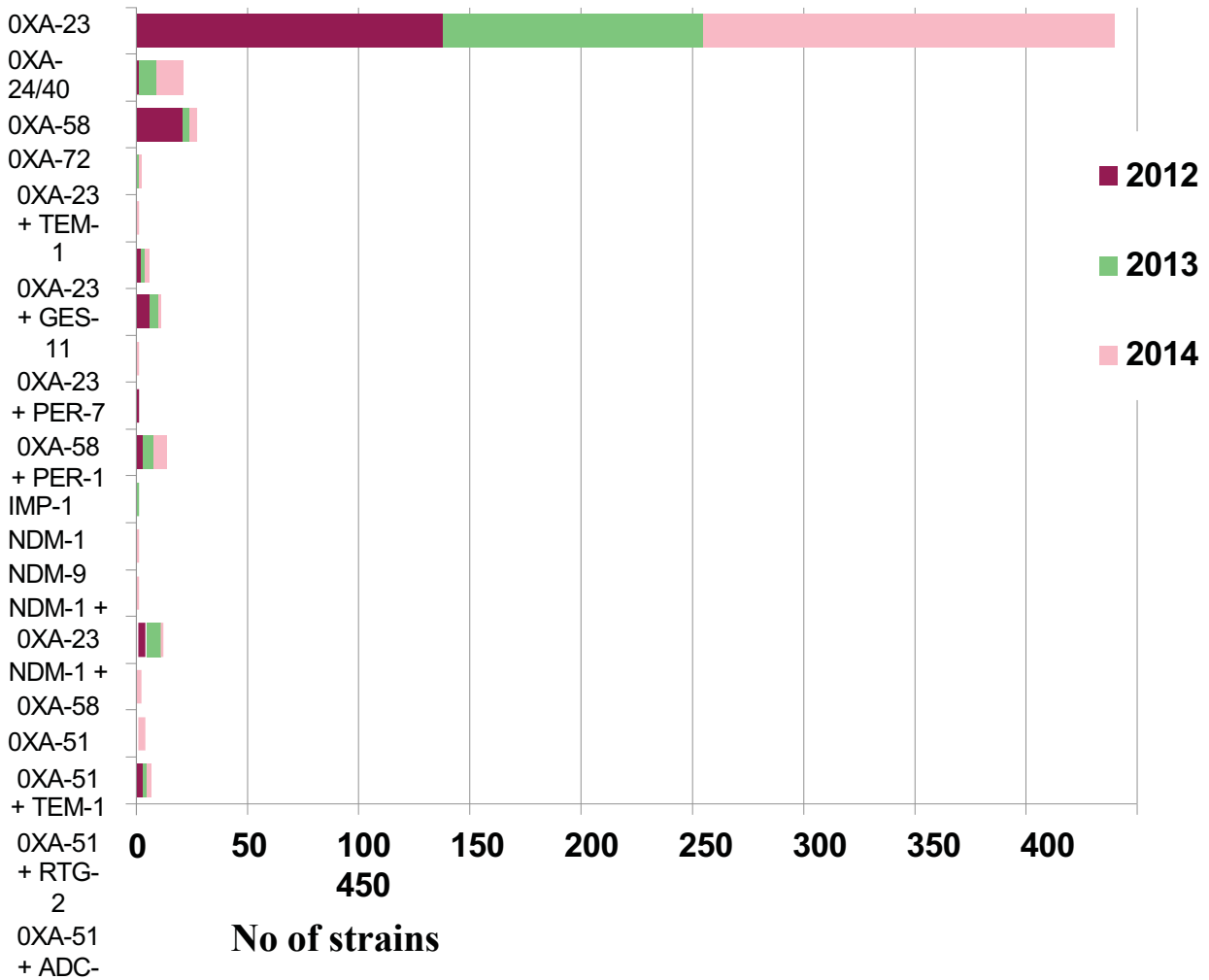
	Cephalosporins - Ceftazidime - Cefepime	Carbapenems - Imipenem - Meropenem
A. baumannii	**AmpC ↑ +++** ESBLs +	**Carbapenemases +++**
P. aeruginosa	**AmpC ↑ +++** ESBLs + Carbapenemases +	**OprD ↓ +++** Carbapenemases +

Carbapenem resistance *A. baumannii*



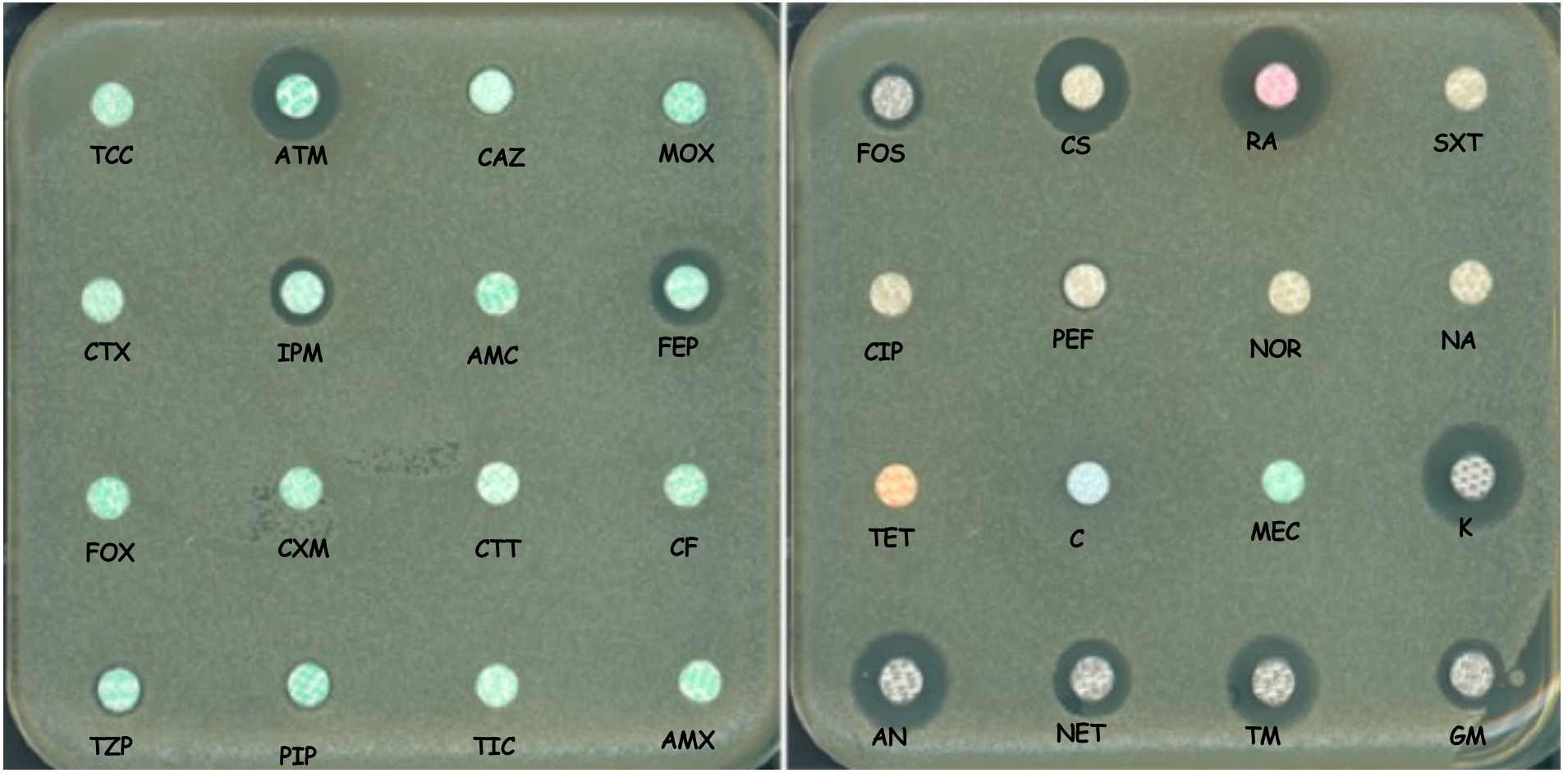
Carbapenemases in *A. baumannii- France*

(*n*=555)

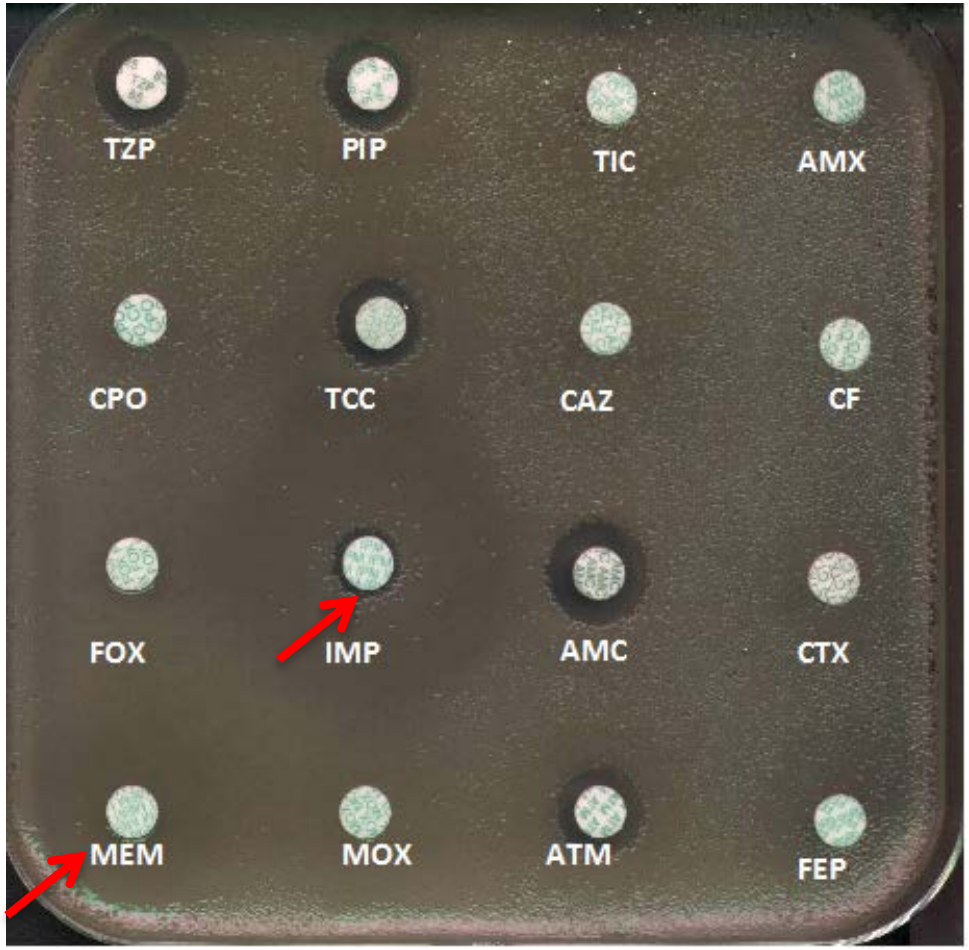


Courtesy Prof P. Plésiat

Multidrug-resistant *A. baumannii* OXA-23



A. baumannii NDM-1



Novel ß-lactam-containing antibiotics

Novel cephalosporin + old inhibitor

Ceftolozane + tazobactam

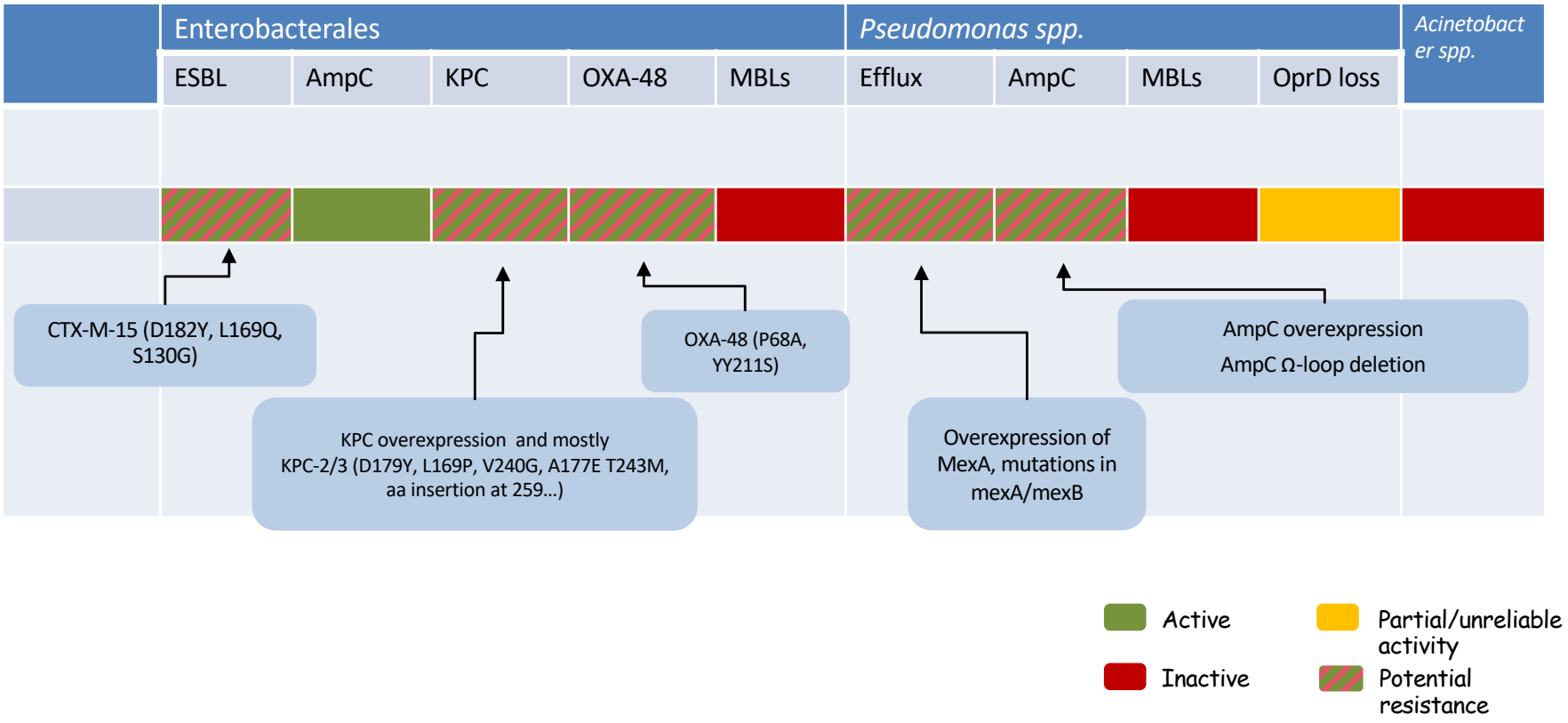
Novel inhibitor + old ß-lactam

Avibactam + ceftazidime
Avibactam + aztreonam
Relebactam + imipenem
Vaborbactam + meropenem

Theoritical activity of novel antibiotics against carbapenemase producers

Antibiotics	Carbapenemases
• Ceftazidime /avibactam	KPC, OXA-48
• Aztreonam/avibactam	KPC, OXA-48, NDM
• Meropenem/varbobactam	KPC, OXA-48
• Imipenem/ relebactam	KPC, OXA-48 ?
• Cefiderocol	KPC, OXA-48, NDM
• Eravacycline	KPC, OXA-48, NDM

Ceftazidime-avibactam



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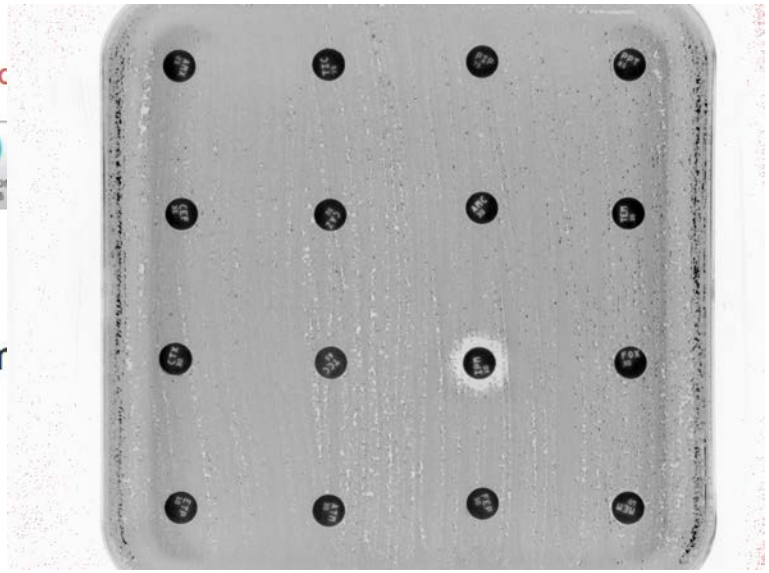


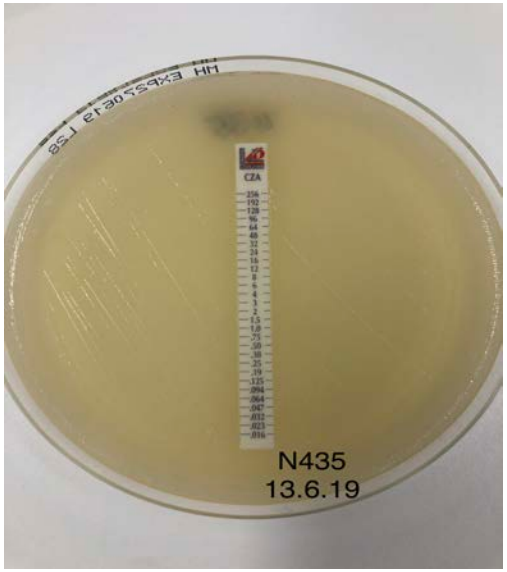
Phenotypic, Biochemical, and Genetic Analysis of KPC-41, a KPC-3 Variant Conferring Resistance to Ceftazidime-Avibactam and Exhibiting Reduced Carbapenemase Activity

Linda Mueller,[a,b,c] Amandine Masseron,[a] Guy Prod'Hom,[c] Tatiana Galperine,[d] Gilbert Greub,[c] Laurent Poirel,[a,b,e] Patrice Nordmann[a,b,c,e]

[a]Emerging Antibiotic Resistance Unit, Medical and Molecular Microbiology, Faculty of Science and Medicine, University of Fribourg, Fribourg, Switzerland
[b]Swiss National Reference Center for Emerging Antibiotic Resistance (NARA), University of Fribourg, Fribourg, Switzerland
[c]Institut for Microbiology, University Hospital Center and University of Lausanne, Lausanne, Switzerland
[d]Infectiology Department, University Hospital Center and University of Lausanne, Lausanne, Switzerland
[e]INSERM European Unit (IAME, France), University of Fribourg, Fribourg, Switzerland

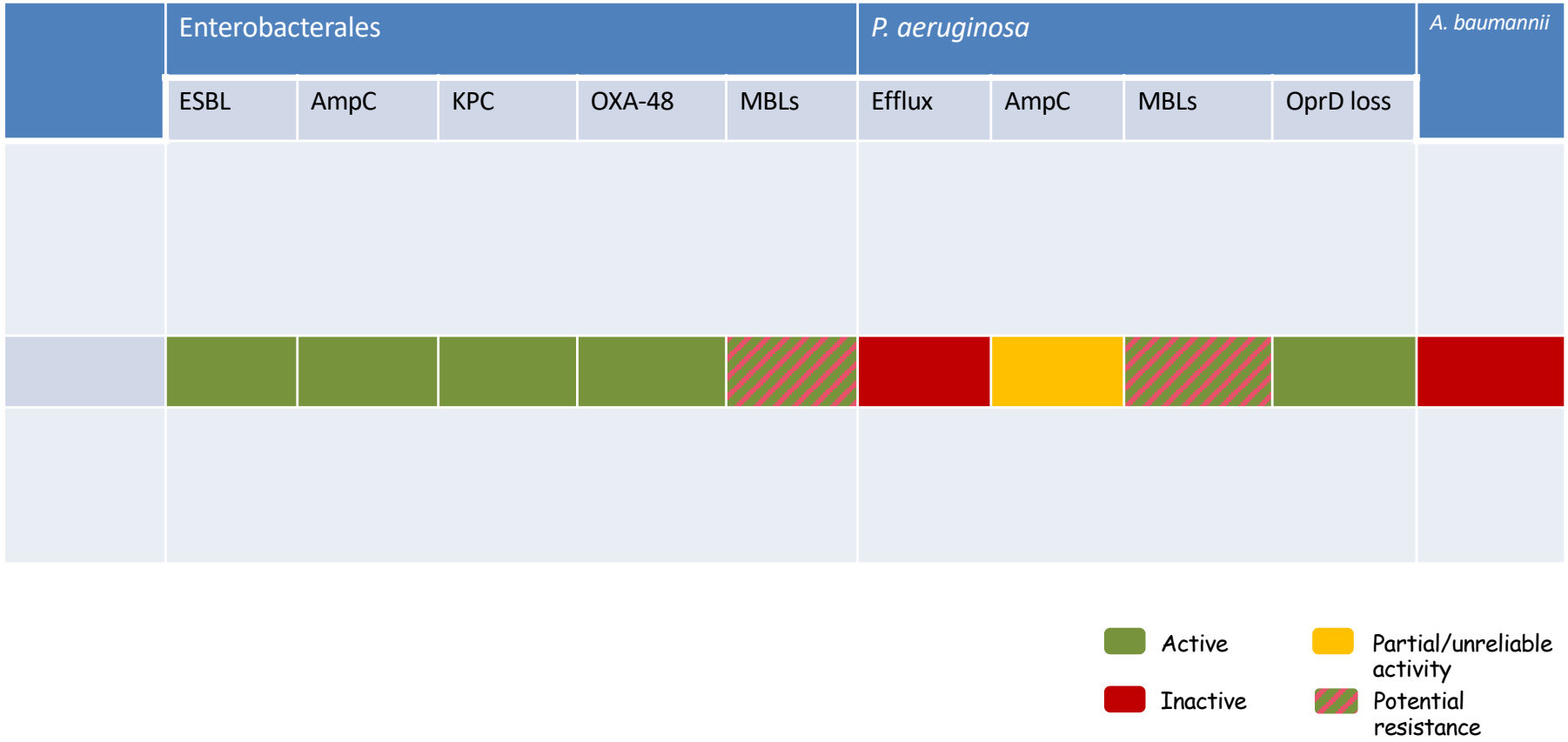
ABSTRACT A novel KPC variant, KPC-41, was identified in a *Klebsiella pneumoniae* clinical isolate from Switzerland. This β-lactamase possessed a 3-amino-acid insertion (Pro-Asn-Lys) located between amino acids 269 and 270 compared to the KPC-3 amino acid sequence. Cloning and expression of the bla_{KPC-41} gene in *Escherichia coli*, followed by determination of MIC values and kinetic parameters, showed that KPC-41, compared to those of KPC-3, has an increased affinity to ceftazidime and a decreased sensitivity to avibactam, leading to resistance to ceftazidime-avibactam once produced in *K. pneumoniae*. Furthermore, KPC-41 exhibited a drastic decrease of its carbapenemase activity. This report highlights that a diversity of KPC variants conferring resistance to ceftazidime-avibactam already circulate in Europe.

2019



Ceftazidime/avibactam

Aztreonam-avibactam



Aztreonam-avibactam resistance

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MECHANISMS OF RESISTANCE

Genetic Features Leading to Reduced Susceptibility to Aztreonam-Avibactam among Metallo-β-Lactamase-Producing *Escherichia coli* Isolates

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[a]Medical and Molecular Microbiology, Faculty of Science and Medicine, University of Fribourg, Fribourg, Switzerland
[b]Swiss National Reference Center for Emerging Antibiotic Resistance (NARA), University of Fribourg, Fribourg, Switzerland
[c]INSERM European Unit (IAME, France), University of Fribourg, Fribourg, Switzerland

Mustafa Sadek and Mario Juhas contributed equally. Author order was determined in order of increasing seniority.

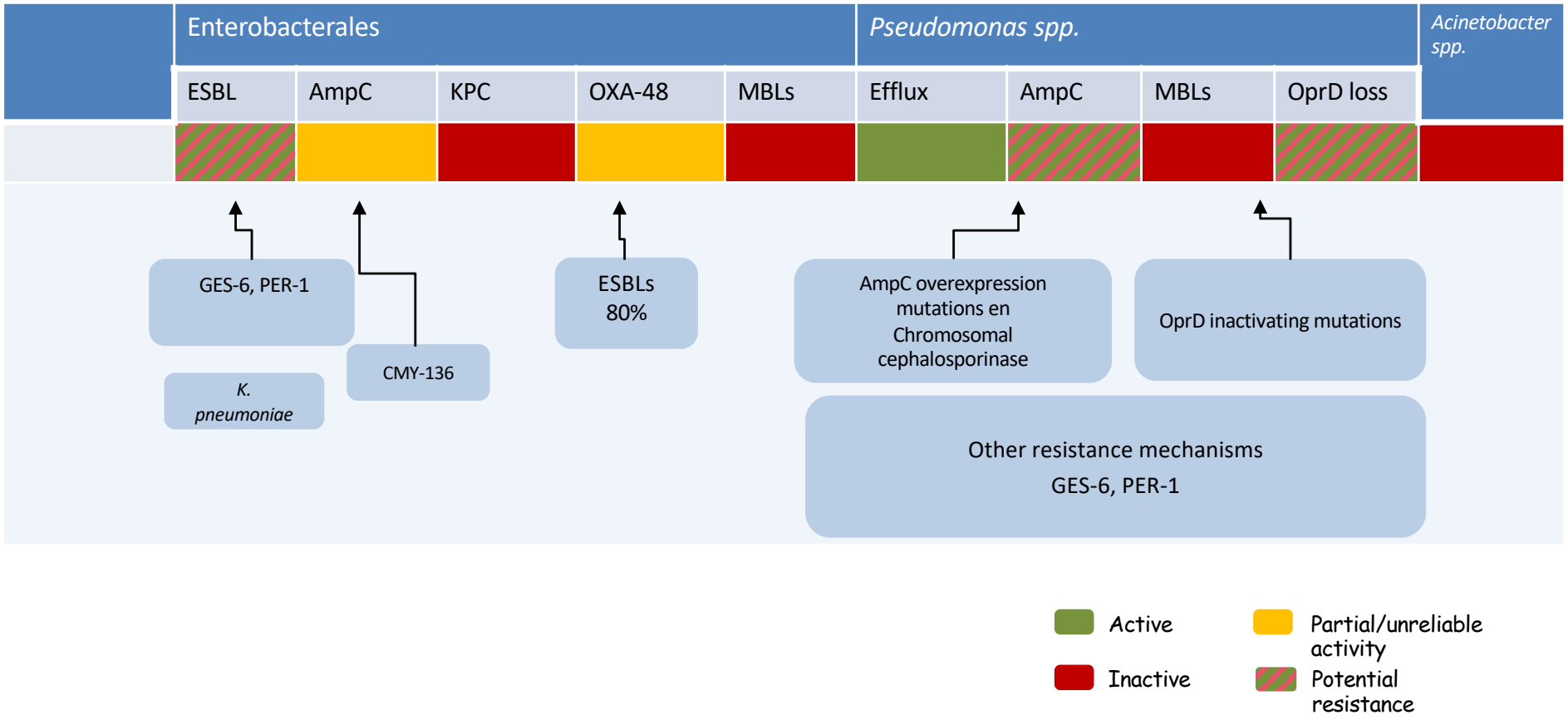
ABSTRACT Metallo-β-lactamase (MBL)-producing *Escherichia coli* isolates resistant to the newly developed β-lactam/β-lactamase inhibitor drug combination aztreonam-avibactam (ATM-AVI) have been reported. Here, we analyzed a series of 118 clinical MBL-producing *E. coli* isolates of various geographical origins for susceptibility to ATM-AVI. The nature of the PBP3 protein sequence and the occurrence of bla_{CMY} genes for susceptibility to ATM-AVI were investigated. We showed here that elevated MICs of ATM-AVI among MBL-producing *E. coli* isolates resulted from a combination of different features, including modification of PBP3 protein sequence through specific amino acid insertions and production of CMY-type enzymes, particularly, CMY-42. We showed here that those insertions identified in the PBP3 sequence are not considered the unique basis of resistance to ATM-AVI, but they significantly contribute to it.

KEYWORDS *Escherichia coli*, aztreonam-avibactam, metallo-β-lactamase, PBP3, NDM, CMY-42

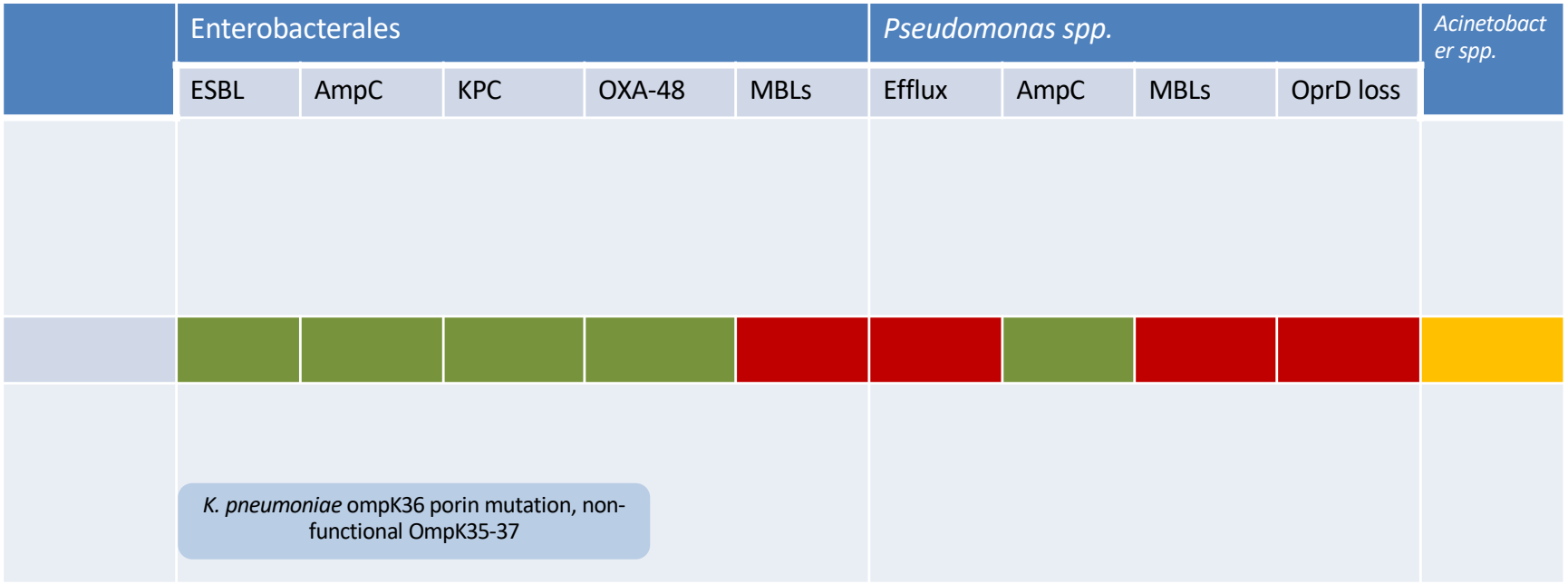
Strain	ST	Metallo-β-lactamase	Other β-lactamase(s)	Origin of isolation[a]	MIC (μg/ml)[b]					PBP3 insertion sequence[c]
					ATM	ATM-AVI	CAZ	CAZ-AVI	IMI	
R-3058	ND	NDM-5	CMY-42	Angola	32	16	>256	>256	32	YRIN
R-461	ND	NDM-1	CMY-42	France	32	16	>256	>256	64	YRIN
R-3038	ND	NDM-5	CMY-42	Angola	32	8	>256	>256	16	YRIN
R-3031	ND	NDM-5	CMY-42	Angola	128	8	>256	>256	32	YRIN
N-185	ND	NDM-5	CMY-42	Switzerland	32	8	256	256	16	YRIN
N-590	167	NDM-5	CMY-42	Switzerland	64	8	>256	>256	32	YRIN
N-1013	361	NDM-5	CMY-42	Switzerland	128	8	>256	>256	64	YRIN
N-1076	940	NDM-5	CMY-42, TEM-1B	Switzerland	64	8	>256	>256	32	YRIN
R-460	ND	NDM-1	CMY-42	France	>256	8	>256	>256	32	YRIN
R-3033	ND	NDM-5	CMY-42	Angola	64	8	>256	>256	16	YRIN
R-3040	ND	NDM-5	CMY-42	Angola	64	8	>256	>256	32	YRIN
R-3043	ND	NDM-5	CMY-42	Angola	64	8	>256	>256	32	YRIN
R-3029	ND	NDM-5	CMY-42, CTX-M group 1	Angola	32	8	>256	>256	32	YRIN
R-3039	ND	NDM-5	CMY-42	Angola	16	8	>256	>256	32	YRIN
R-3048	ND	NDM-5	CMY-42	Angola	16	8	>256	>256	32	YRIN
R-3054	ND	NDM-5	CMY-42	Angola	16	8	>256	>256	32	YRIN
N-57	ND	NDM-5	CMY-42	Switzerland	32	8	>256	256	32	YRIK
R-466	405	NDM-4	CMY-42, CTX-M-15, OXA-1	Cameroon	>256	8	>256	>256	16	YRIK
R-2222	ND	NDM-4	CMY-42	France	>256	8	>256	256	64	YRIK
R-474	ND	NDM-7	CMY-6	France	16	4	>256	>256	64	YRIN
N-6	ND	NDM-5	CMY-16	Switzerland	128	4	256	128	32	YRIN

2020

Ceftolozane-tazobactam

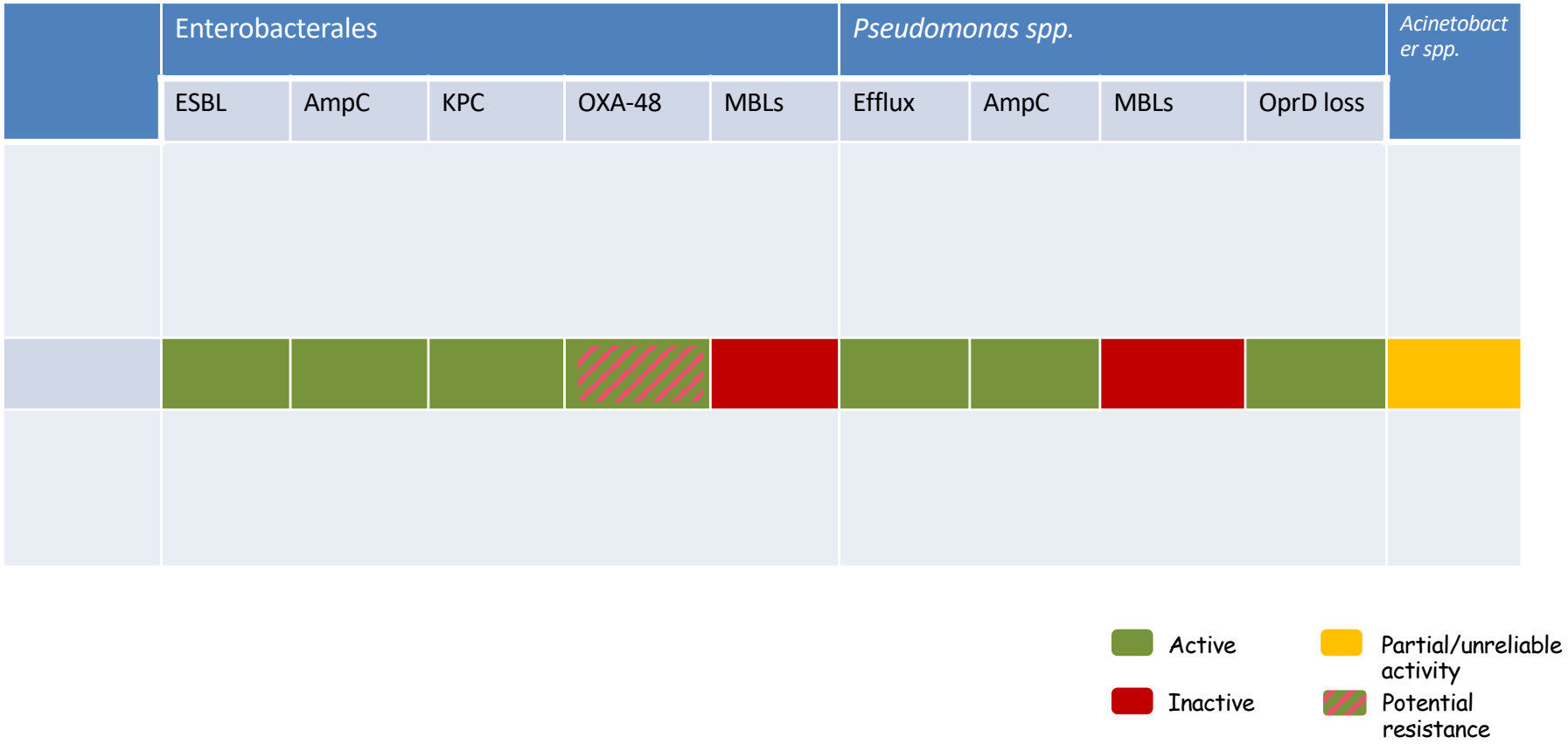


Meropenem-vaborbactam

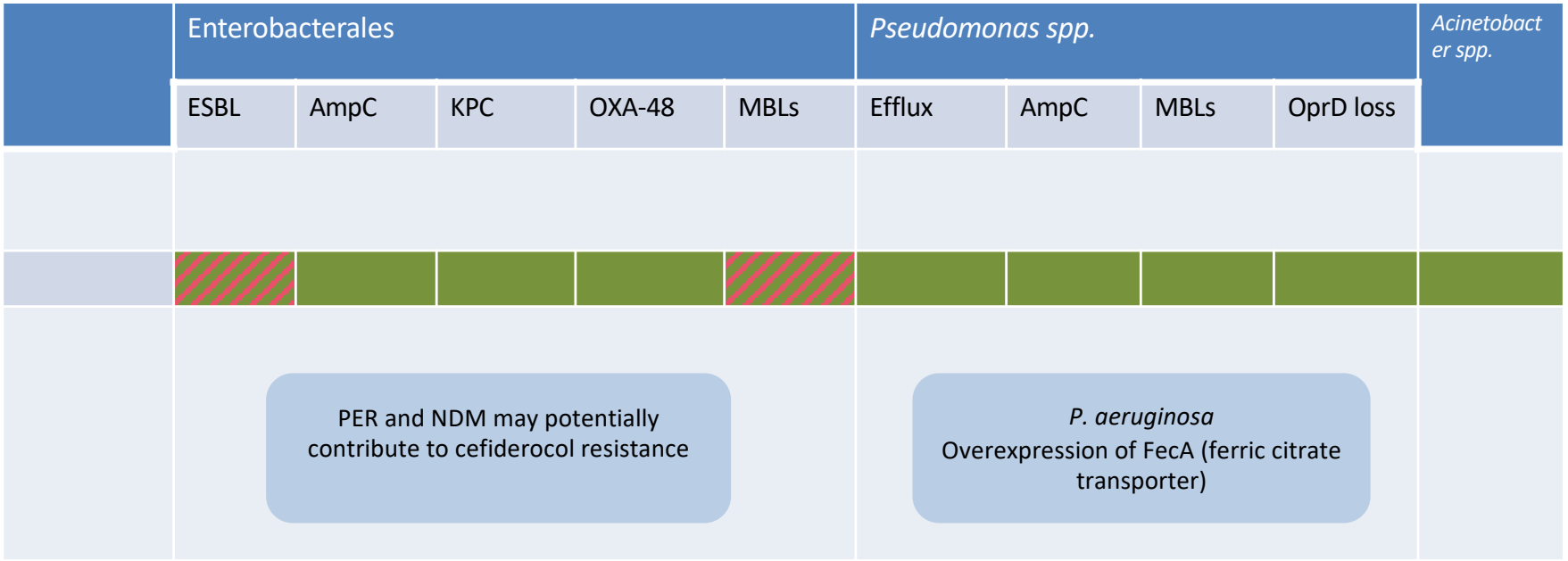


Active
Inactive
Partial/unreliable activity
Potential resistance

Imipenem-relebactam



Cefiderocol



Other antibiotics

Antibiotic	Enterobacterales				*P. aeruginosa*				*A. baumannii*
	ESBL	KPC	OXA-48	MBLs	Efflux	AmpC	MBLs	OprD loss	
Eravacycline									
Plazomicin									
Sulopenem		?	?	?	?	?	?	?	?
Taniborbactam-cefepime					?				-
Enmetazobactam-cefepime			?	?	?	?	?	?	?

Active
Inactive
Partial/unreliable activity
Potential resistance

WHO's 'priority pathogens' list highlights urgent need for new drugs

Feb 27, 2017

Priority 1: Critical

•Enterobacteriaceae, carbapenem-resistant, ESBL-producing.

•*Pseudomonas aeruginosa*, carbapenem-resistant.

•*Acinetobacter baumannii*, carbapenem-resistant.

•

Priority 2: High

• *Enterococcus faecium*, vancomycin-resistant.

• *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and resistant.

• *Helicobacter pylori*, clarithromycin-resistant.

• Campylobacter spp., fluoroquinolone-resistant.

• Salmonella, fluoroquinolone-resistant.

•*Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant.

Priority 3: Medium

•*Streptococcus pneumoniae*, penicillin-non-susceptible.

•*Haemophilus influenzae*, ampicillin-resistant.

•Shigella spp., fluoroquinolone-resistant.

https://www.who.int/news-room/detail/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed. Last accessed 05.11.2019